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(71) Applicant *(for all designated States except US)*: EXELIXIS, INC. [US/US]; 210 East Grand Avenue, South San Francisco, California 94080 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: LAMB, Peter [US/US]; 814 Mandon Boulevard, Oakland, CA 94610 (US).

(74) Agents: WADE, Janice V. et al.; Exelixis, Inc., 210 East Grand Avenue, South San Francisco, CA 94080 (US).

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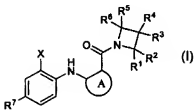

(I)

(57) Abstract: The present invention provides methods of treating cancer by administering a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments.

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METHODS OF USING MEK INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to methods of treating cancer with a compound that inhibits protein kinase enzymatic activity and the resultant modulation of cellular activities (such as proliferation, differentiation, programmed cell death, migration, chemoinvasion and metabolism) in combination with anticancer agents.

State of the Art

[0002] Improvements in the specificity of agents used to treat various disease states such as cancer, metabolic, and inflammatory diseases is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins at the hydroxy groups of tyrosine, serine and threonine residues of proteins. The kinase complement of the human genome contains 518 putative protein kinase genes (Manning et al, Science, (2002), 298, 1912). The consequences of this activity include effects on cell differentiation, proliferation, transcription, translation, metabolism, cell cycle progression, apoptosis, metabolism, cytoskeletal rearrangement and movement; *i.e.*, protein kinases mediate the majority of signal transduction in eukaryotic cells. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to cancer. Chromosomal mapping has revealed that over 200 kinases map to disease loci, including cancer, inflammatory and metabolic disease.

[0004] Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1),

HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and -beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (Flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al. (1994) DN&P 7(6): 334-339, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Syk/Zap70, Fes/Fps, Fak, Jak, and Ack. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen (1993) Oncogene, 8:2025-2031, which is hereby incorporated by reference.

[0007] Serine-threonine kinases play critical roles in intracellular signal transduction and include multiple families, such as STE, CKI, AGC, CAMK, and CMGC. Important subfamilies include, the MAP kinases, p38, JNK and ERK, which modulate signal transduction resulting from such diverse stimuli as mitogenic, stress, proinflammatory and antiapoptotic pathways. Members of the MAP kinase subfamily have been targeted for therapeutic intervention, including p38a, JNK isozymes and Raf.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, such as immunological disorders, metabolic and cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0009] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0010] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc Technol* **2001** *6*, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0011] One particularly attractive target for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is MEK. Inhibition of MEK1 (MAPK/ERK Kinase) is a promising strategy to control the growth of tumors that are dependent on aberrant ERK/MAPK pathway signaling (Solit et al., 2006; Wellbrock et al., 2004). The MEK-ERK signal transduction cascade is a conserved pathway which regulates cell growth, proliferation, differentiation, and apoptosis in response to growth factors, cytokines, and hormones. This pathway operates downstream of Ras which is often upregulated or mutated in human tumors. It has been demonstrated that MEK is a critical effector of Ras function. The ERK/MAPK pathway is upregulated in 30% of all tumors and oncogenic activating mutations in K-Ras and B-Raf have been identified in 22% and 18% of all cancers respectively (Allen et al., 2003; Bamford S, 2004; Davies et al., 2002; Malumbres and Barbacid, 2003). A large portion of human cancers, including 66% (B-Raf) of malignant melanomas, 60% (K-Ras) and 4% (B-Raf) of pancreatic cancers, 50% of colorectal cancers (colon, in particular, K-Ras: 30%, B-Raf: 15%), 20% (K-Ras) of lung cancers, 27% (B-Raf) papillary and anaplastic thyroid cancer, and 10-20% (B-Raf) of endometriod ovarian cancers, harbor activating Ras and Raf mutations. Other cancers that may be treatable by inhibiting the ERK/MAPK pathway include kidney cancer (Rika Hoshino, et. al. Oncogene 21 January 1999, Volume 18, Number 3, Pages 813-822), breast cancer (Santen RJ, et. al. *Steroid Biochem Mol Biol* **2002**, 80239), multiple myeloma Hu L

et. al. *Blood* **2003**, *101*, 3126), ovarian cancer Nicosia SV et. al. *Hematol Oncol Clin North Am* **2003**, 17 927), and AML (Milella M et. al. *Curr Pharm Des* **2005**, *11*, 2779).

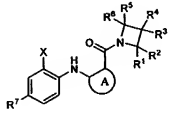
[0012] It has been shown that inhibition of the ERK pathway, and in particular inhibition of MEK kinase activity, results in anti-metastatic and anti-angiogenic effects largely due to a reduction of cell-cell contact and motility as well as downregulation of vascular endothelial growth factor (VEGF) expression. Furthermore, expression of dominant negative MEK, or ERK reduced the transforming ability of mutant Ras as seen in cell culture and in primary and metastatic growth of human tumor xenografts *in vivo*. Therefore, the MEK-ERK signal transduction pathway is an appropriate pathway to target for therapeutic intervention.

[0013] It is well established that combining treatments with different mechanisms of action often leads to enhanced anti-tumor activity as compared to single treatments administered alone. This is true for combinations of chemotherapies (e.g. Kyrgiou M. et. al. *J Natl Cancer Inst* **2006**, *98*, 1655) and combinations of antibodies and chemotherapy (e.g. Pasetto LM et. al. *Anticancer Res* **2006**, *26*, 3973.

SUMMARY OF THE INVENTION

[0014] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include cancer. The invention is directed to methods of treating these diseases by administering a Compound of Formula I in combination with one or more treatment(s).

[0015] One aspect of the Invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a compound of Formula I:



I

or a pharmaceutically acceptable salt or solvate, thereof; or administering a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent in combination with one or more treatment(s) selected from surgery, one or more chemotherapeutic agent(s), one or more of the hormone therapy(s), one or more of the antibody(s), hypothermia therapy, radioactive iodine therapy, and radiation wherein the Compound of Formula I is that where A, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Group A, Group B, Group C, or Group D:

Group A:

A is arylene optionally substituted with one, two, three or four groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ and $-NR^8C(O)R^{8'}$;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0, 1, or 2;

R^7 is hydrogen, halo or alkyl;

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxycarbonyl, optionally substituted arylalkyl, optionally substituted arylalkyloxy, optionally substituted arylalkyloxycarbonyl, nitro, cyano, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{34}SO_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-SO_2NR^{35}R^{35a}$ (where R^{35} is hydrogen or alkyl and R^{35a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl);

R^9 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally susbstituted with one, two, three, four, or five groups selected from halo, hydroxy, alkyl, haloalkyl, haloalkoxy, amino, alkylamino, and dialkylamino;

R^{25} and R^{25b} are independently hydrogen, alkyl, alkenyl, optionally sbustituted cycloalkyl, or optionally substituted aryl; and

R^{25a} is hydrogen, alkyl, or alkenyl;

Group B:

A is heteroarylene optionally substituted with one, two, three, or four groups selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, cyano,

amino, alkylamino, dialkylamino, haloalkyl, alkylsulfonylamino, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, alkenyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or alkylcarbonylamino; where R^{19} is hydrogen, alkyl, or alkenyl; and where each alkyl and alkenyl, either alone or as part of another group within R^{10}, R^{12}, R^{14}, R^{16}, and R^{19} is independently optionally substituted with halo, hydroxy, or alkoxy;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

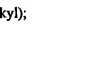
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where

n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl);

Group C:

A is



(a)

where R^{10} is hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ and $-NR^8C(O)R^{8'}$;

R^{10a} is hydrogen, alkyl, or alkenyl;

Y^1 is =CH- or =N-;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl,

alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

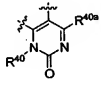
R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently

hydrogen, alkyl, or hydroxyalkyl), and -C(O)NHR^{33} (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl); or

Group D:

A is

(b) or



(c)

R^{40} and R^{40a} are independently hydrogen or alkyl;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, -NR^{8}R$^{8'}$, -OR^8, -NHS(O)$_2$R^8, -CN, -S(O)$_m$R^8, -S(O)$_2$NR^{8}R$^{8'}$, -C(O)R^8, -C(O)OR^8, -C(O)NR^{8}R$^{8'}$, -NR^{8}C(O)OR$^{8'}$, -NR^{8}C(O)NR$^{8'}$R$^{8''}$, -NR^{8}C(O)OR$^{8'}$, -NR^{8}C(O)R$^{8'}$, -CH$_2$N(R^{25})(NR^{25a}R^{25b}), -CH$_2$NR^{25}C(=NH)(NR^{25a}R^{25b}), -CH$_2$NR^{25}C(=NH)(N(R^{25a})(NO$_2$), -CH$_2$NR^{25}C(=NH)(N(R^{25a})(CN), -CH$_2$NR^{25}C(=NH)(R^{25}), -CH$_2$NR^{25}C(NR^{25a}R^{25b})=CH(NO$_2$), alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, -OR^8, -NR^{8}R$^{8'}$, -NR^{8}S(O)$_2$R^9, -CN, -S(O)$_m$R^9, -C(O)R^8, -C(O)OR^8, -C(O)NR^{8}R$^{8'}$, -NR^{8}C(O)NR$^{8'}$R$^{8''}$, -NR^{8}C(O)OR$^{8'}$ and -NR^{8}C(O)R$^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl).

DETAILED DESCRIPTION OF THE INVENTION

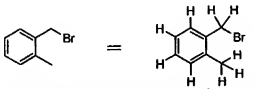
Definitions for the Mek Compound

[0016] The following terms have the indicated meanings throughout:

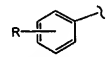
[0017] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, and "---" means a single bond and optionally a double bond. When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four.

[0018] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic

below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

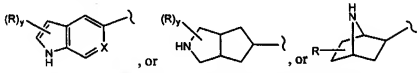


[0019] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



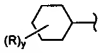
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0020] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

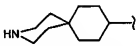


then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0021] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0022] "Acyl" means a -C(O)R radical where R is optionally substituted alkyl, optionally substituted alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, benzoyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

[0023] "Acylamino" means a -NRR' group where R is acyl, as defined herein, and R' is hydrogen or alkyl.

[0024] "Administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., surgery, radiation, and chemotherapy, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[0025] "Alkenyl" means a means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one double bond, e.g., ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

[0026] "Alkenylcarbonyl" means a -C(O)R group where R is alkenyl, as defined herein.

[0027] "Alkenyloxycarbonyl" means a -C(O)OR group where R is alkenyl, as defined herein.

[0028] "Alkoxy" means an -OR group where R is alkyl group as defined herein. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0029] "Alkoxyalkyl" means an alkyl group, as defined herein, substituted with at least one, preferably one, two, or three, alkoxy groups as defined herein. Representative examples include methoxymethyl and the like.

[0030] "Alkoxycarbonyl" means a -C(O)OR group where R is alkyl as defined herein.

[0031] "Alkoxycarbonylamino" means a -NR'R" group where R' is hydrogen, alkyl, hydroxy, or alkoxy and R" is alkoxycarbonyl, as defined herein.

[0032] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

[0033] "Alkylamino" means a -NHR radical where R is alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *iso*-butylamino, *tert*-butylamino, or methylamino-N-oxide, and the like.

[0034] "Alkylaminoalkyl" means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[0035] "Alkylaminocarbonyl" means a -C(O)R group where R is alkylamino, as defined herien.

[0036] "Alkylcarbonyl" means a -C(O)R group where R is alkyl, as defined herein.

[0037] "Alkylcarbonylamino" means a -NRR' group where R is hydrogen or alkyl as defined herein and R' is alkylcarbonyl, as defined herein.

[0038] "Alkylcarbonyloxy" means an -OC(O)R group where R is alkyl, as defined herein.

[0039] "Alkylsulfonylamino" means a $-NRS(O)_2R'$ group where R is hydrogen or alkyl as defined herein, and R' is alkyl, as defined herein.

[0040] "Alkynyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one triple bond and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

[0041] "Aminoalkyl" means an alkyl group substiuted with at least one amino group and in another embodiment, one, two or three amino groups.

[0042] "Aminocarbonyl" means a $-C(O)NH_2$ group.

[0043] "Aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Representative examples include phenyl, naphthyl, and indanyl, and the like.

[0044] "Arylene" means a divalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Representative examples include phenylene, naphthylene, and indanylene, and the like.

[0045] "Arylalkyl" means an alkyl group, as defined herein, substituted with one or two aryl groups, as defined herein. Examples include benzyl, phenethyl, and the like.

[0046] "Carboxy ester" means a -C(O)OR group where R is lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, aryl or arylalkyl, each of which is defined herein. Representative examples include methoxycarbonyl, ethoxycarbonyl, and benzyloxycarbonyl, and the like.

[0047] "Cycloalkyl" means a monocyclic or fused bicyclic, saturated or partially unsaturated (but not aromatic), monovalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. The term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, or cyclohex-3-enyl, and the like.

[0048] "Dialkylamino" means a -NRR' radical where R and R' are alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.

[0049] "Dialkylaminoalkyl" means an alkyl group substituted with one or two dialkylamino groups, as defined herein.

[0050] "Dialkylaminocarbonyl" means a -C(O)R group where R is dialkylamino, as defined herien.

[0051] "Fused-polycyclic" or "fused ring system" means a polycyclic ring system that contains fused rings and, unless otherwise indicated, can contain bridged rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic. In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (*i.e.* saturated ring structures) can contain two substitution groups.

[0052] "Haloalkoxy" means an -OR' group where R' is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

[0053] "Halogen" or "halo" means fluoro, chloro, bromo and iodo.

[0054] "Haloalkyl" means an alkyl group, as defined herein, that is substituted with one or more halogens, preferably one to five halo atoms. Representative examples include trifluoromethyl, difluoromethyl, 1-chloro-2-fluoro-ethyl, and the like.

[0055] "Heteroaryl" means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, $-S(O)_n-$ (n is 0, 1, or 2), -N-, $-N(R^x)-$, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R^x is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. Unless stated otherwise, the valency may be located on

any atom of any ring of the heteroaryl group, valency rules permitting. In particular, when the point of valency is located on the nitrogen, R^x is absent. The term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, 1,3,5-triazolyl, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzodioxol-4-yl, benzofuranyl, cinnolinyl, indolizinyl, naphthyridin-3-yl, phthalazin-3-yl, phthalazin-4-yl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, oxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothienyl, and the derivatives thereof, or N-oxide or a protected derivative thereof.

[0056] "Heteroarylene" means a monocyclic, fused bicyclic, or fused tricyclic, divalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, $-S(O)_n-$ (n is 0, 1, or 2), -N-, $-N(R^{19})-$, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R^{19} is hydrogen, alkyl, or alkenyl. Unless stated otherwise, the valencies may be located on any atom of any ring of the heteroarylene group, valency rules permitting. In particular, when the point of valency is located on the nitrogen, R^x is absent. The term heteroaryl includes, but is not limited to, thien-diyl, benzo[*d*]isoxazol-diyl, benzo[*d*]isothiazol-diyl, 1*H*-indazol-diyl (optionally substituted at the N1 position with R^{19}), benzo[*d*]oxazol-diyl, benzo[*d*]thiazol-diyl, 1*H*-benzo[*d*]imidazol-diyl (optionally substituted at the N1 position with R^{19}), 1*H*-benzo[*d*][1,2,3]triazol-diyl (optionally substituted at the N1 position with R^{19}), imidazo[1,2-*a*]pyridin-diyl, cinnolin-diyl, quinolin-diyl, pyridin-diyl, 1-oxido-pyridin-diyl, [1,2,4]triazolo[4,3-a]pyridin-diyl, and 2,3-dihydroimidazo[1,2-a]pyridin-diyl, and the like.

[0057] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more (and in another embodiment, one, two, three, or four) ring heteroatoms independently selected from O, $S(O)_n$ (n is 0, 1, or 2), N, $N(R^y)$ (where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl), the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. When the point of valency is located on a nitrogen atom, R^y is absent. The term heterocycloalkyl includes, but is not limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, and tetrahydropyranyl, and the derivatives thereof and N-oxide or a protected derivative thereof.

[0058] "Hydroxyalkyl" means an alkyl, as defined herein, substituted with at least one, preferably one, two, or three, hydroxy group(s), provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl, and the like.

[0059] "Hydroxyamino" means a -NH(OH) group.

[0060] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that with respect to any molecule described as containing one or more optional substituents, only sterically practical and/or

synthetically feasible compounds are meant to be included. "Optionally substituted " refers to all subsequent modifiers in a term. So, for example, in the term "optionally substituted arylC_{1-8} alkyl," both the "C_{1-8} alkyl" portion and the "aryl" portion of the molecule may or may not be substituted. A list of exemplary optional substitutions is presented below in the definition of "substituted."

[0061] "Optionally substituted alkoxy" means an -OR radical where R is optionally substituted alkyl as defined herein. Representative examples include $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH(NH_2)CH_3$, and the like.

[0062] "Optionally substituted alkyl" means an alkyl radical, as defined herein, optionally substituted with one or more group(s) (and in another embodiment one, two, three, four, or five groups) independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, halo, hydroxy, hydroxyalkoxy, carboxy, alkylcarbonylamino, alkylcarbonyloxy, $-S(O)_{0-2}$-alkyl, $-S(O)_{0-2}$-alkenyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, $-NR^cS(O)_2$-alkyl (where R^c is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and $-C(O)NR^aR^b$ (where R^a and R^b are independently hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

[0063] "Optionally substituted aryl" means an aryl group, as defined herein, which is optionally substituted with one, two, three, four, of five groups selected from halo, haloalkyl, haloalkoxy, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, carboxy, carboxy ester, amino, alkylamino, dialkylamino, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -C(O)NR'R" (where R' is hydrogen or alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and $-NHS(O)_2R'$ (where R' is alkyl, aryl, or heteroaryl).

[0064] "Optionally substituted arylalkyl means an alkyl group substituted with one or two optionally substituted aryl group(s) as defined herein.

[0065] "Optionally substituted arylalkyloxy" means an -OR group where R is optionally substituted arylalkyl, as defined herein.

[0066] "Optionally substituted arylalkyloxycarbonyl" means a -C(O)R group where R is optionally substituted arylalkyloxy, as defined herein.

[0067] "Optionally substituted aryloxy" means an -OR group where R is optionally substituted aryl, as defined herein.

[0068] "Optionally substituted aryloxycarbonyl" means a -C(O)R group where R is optionally substituted aryloxy as defined herein.

[0069] "Optionally substituted cycloalkyl" means a cycloalkyl radical, as defined herein, that is optionally substituted with one, two, three, or four groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, halo, haloalkyl, haloalkoxy, oxo, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, dialkylamino, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl dialkylaminoalkyl, carboxy, carboxy ester, cycloalkyl, hydroxyalkyl, -C(O)NR'R" (where R' is hydrogen, alkyl, hydroxy, or alkoxy and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and -NHS(O)$_2$R' (where R' is alkyl, aryl, or hetercyclyl).

[0070] "Optionally substituted cycloalkyloxycarbonyl" means a -C(O)OR group where R is optionally substituted cycloalkyl as defined herein.

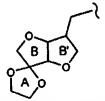
[0071] "Optionally substituted heteroaryl" means a heteroaryl group, as defined herein, optionally substituted with one, two, three, four, or five groups selected from halo, haloalkyl, haloalkoxy, alkyl, alkenyl, alkynyl, alkoxy, hydroxy, oxo (valency rules permitting), carboxy, carboxy ester, amino, alkylamino, dialkylamino, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, heteroaryl, optionally substituted aryl, -C(O)NR'R" (where R' is hydrogen or alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and -NHS(O)$_2$R' (where R' is alkyl, aryl, or heteroaryl).

[0072] "Optionally substituted heterocycloalkyl" means a heterocycloalkyl ring, as defined herein, optionally substituted with one, two, three, four, or five groups

selected from halo, haloalkyl, haloalkoxy, hydroxy, oxo, alkyl, alkenyl, alkynyl, alkoxy, optionally substituted cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, alkylaminoalkyl, dialkylaminoalkyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, -C(O)NR'R" (where R' is hydrogen or alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), amino, alkylamino, dialkylamino, and -$NHS(O)_2R'$ (where R' is alkyl, aryl, or heteroaryl).

[0073] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0074] "Spiro", "Spirocyclyl" or "spiro ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto.



[0075] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

Definitions for the Compound of formula 100

[0076] The terms used to describe the scope of formula 100 are defined in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004) which is herein incorporated by reference. For example "optionally substituted alkyl" for formula 100 has the meaning given in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004). Whenever a compound of formula 100 is described in this application, whether by structure or by use of the term "formula 100," the terms used

to describe that compound are defined by WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004).

Definitions for the Compound of formula 101

[0077] The terms used to describe the scope of formula 101 are defined in WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 101 has the meaning given in WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789). Whenever a compound of formula 101 is described in this application, whether by structure or by use of the term "formula 101," the terms used to describe that compound are defined by WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789).

Definitions for the Compound of formula A-B-C

[0078] The terms used to describe the scope of formula A-B-C are defined in WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula A-B-C has the meaning given in WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336). Whenever a compound of formula A-B-C is described in this application, whether by structure or by use of the term "formula A-B-C," the terms used to describe that compound are defined by WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336).

Definitions for the Compound of formula 103

[0079] The terms used to describe the scope of formula 103 are defined in WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 103 has the meaning given in WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140). Whenever a compound of formula 103 is described in this application, whether by structure or by use of the term "formula 103," the terms used to describe that compound are defined by WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140).

Definitions for the Compound of formula 105

[0080] The terms used to describe the scope of formula 105 are defined in WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 105 has the meaning given in WO 2006/074057 (US Nat'l Stage Application

Serial No. 11/722,719). Whenever a compound of formula 105 is described in this application, whether by structure or by use of the term "formula 105," the terms used to describe that compound are defined by WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719).

Definitions for the Compound of formula 107

[0081] The terms used to describe the scope of formula 107 are defined in WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555) which is herein incorporated by reference. For example "optionally substituted aryl" for formula 107 has the meaning given in WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555).Whenever a compound of formula 107 is described in this application, whether by structure or by use of the term "formula 107," the terms used to describe that compound are defined by WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555).

Definitions for the Compound of formula 108

[0082] The terms used to describe the scope of formula 108 are defined in WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173) which is herein incorporated by reference. For example "optionally substituted aryl" for formula 108 has the meaning given in WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173). Whenever a compound of formula 108 is described in this application, whether by structure or by use of the term "formula 108," the terms used to describe that compound are defined by WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173).

Definitions for the Compound of formula 109

[0083] The terms used to describe the scope of formula 109 are defined in WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291 which is herein incorporated by reference. For example "optionally substituted aryl" for formula 109 has the meaning given in WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291. Whenever a compound of formula 109 is described in this application, whether by structure or by use of the term "formula 109," the terms used to describe that compound are defined by WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291.

Other Definitions

[0084] "AKT inhibitor" includes, for example, LY294002, PKC412, and compounds described in WO 2006/071819 and WO05/117909.

[0085] "Alkylating agent(s)" includes, for example, one or more of the following: Chlorambucil, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan, Carmustine, Streptozocin, Fotemustine, Lomustine, Streptozocin, Carboplatin, Cisplatin, Oxaliplatin, BBR3464, Busulfan, Dacarbazine, Mechlorethamine, Procarbazine, Temozolomide, ThioTEPA, and Uramustine.

[0086] "Antibody(s)" includes, for example, one or more of the following: IGF1R antibody (including, for example, αIGF-1R A12 MoAb, 19D12, h7C10 and CP-751871), Alemtuzumab, Bevacizumab (Avastin®), Cetuximab (Erbitux®), Gemtuzumab, Gemtuzumab ozogamicin, Ibritumomab (tiuxetan), Panitumumab, Rituximab, Tositumomab, and Trastuzumab (Herceptin®).

[0087] "Antimetabolite(s)" include, for example, methotrexate, Pemetrexed, Raltitrexed, Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Thioguanine, Capecitabine, Cytarabine, fluorouracil (administered with or without leucovorin or folinic acid), and Gemcitabine.

[0088] "Antimicrotubule agent(s)" includes, for example, Vincristine,Vinblastine, Vinorelbine, Vinflunine, and Vindesine.

[0089] "Aromatase inhibitor(s)" includes, for example, one or more of the following: Aminoglutethimide, Anastrozole (Arimidex®), Letrozole (Femara®), Exemestane (Aromasin®), and Formestane (Lentaron®).

[0090] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney

(adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Adrenal Glands: neuroblastoma; and breast cancer. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0091] "cMET inhibitor" includes, for example, compounds described in WO06/108059, WO 2006/014325, and WO 2005/030140.

[0092] "EGFR inhibitor"includes, for example, one or more of the following: Lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788 and HKI-272, EKB-569, CI1033, and compounds described in WO 2004/006846 and WO 2004/050681.

[0093] "ErbB2 inhibitor" includes, for example, Lapatinib (GW572016), and PKI-166.

[0094] "Hormone therapy" or "hormonal therapy" includes, for example, treatment with one or more of the following: steroids (e.g. dexamethasone), finasteride, tamoxifen, and an aromatase inhibitor.

[0095] "HSP90 inhibitor(s)" includes, for example, 17-AAG, 17-DMAG, Geldanamycin, 5-(2,4-dihydroxy-5-isopropylphenyl)-*N*-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide [NVP-AUY922 (VER 52296)], 6-chloro-9-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-9*H*-purin-2-amine (CNF2024, also named BIIB021), compounds disclosed in WO2004072051 (which is herein incorporated by reference), compounds disclosed in WO2005028434 (which is herein incorporated by reference), compounds disclosed in WO2007035620 (which is herein incorporated by reference) and compounds disclosed in WO2006091963 (which is herein incorporated by reference).

[0096] "Hypothermia therapy" is a type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs.

[0097] "IGF1R inhibitor(s)" include, for example, Tyrphostin AG 1024 and compounds described in WO06/074057.

[0098] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0099] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases

phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (*i.e.* tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[00100] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[00101] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In an embodiment the patient is a mammal, and in another embodiment the patient is human.

[00102] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[00103] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[00104] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferable salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethaminc, *N*-methylglucaminc, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[00105] "Platin(s)," and "platin-containing agent(s)" include, for example, cisplatin, carboplatin, and oxaliplatin.

[00106] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis

in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[00107] "Raf inhibitor(s)" include, for example, sorafenib and compounds described in WO 2005/112932.

[00108] "Rapamycin analogue(s)" include for example, CCI-779, AP23573, RAD001, TAFA93, and compounds described in WO 2004/101583 and US 7,160,867 which are each incorporated herein by reference in their entireties.

[00109] "Receptor Tyrosine Kinase inhibitor(s)" includes, for example, inhibitors of AKT, EGFR, ErbB2, IGF1R, Met, Raf, and VEGFR2. Examples of receptor tyrosine kinase inhibitors can be found in WO 2006/108059 (US Nat'l Stage Application Serial No. 11/910,720), WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719), WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291), WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140), WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173), WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336), WO 2004/050681 US Nat'l Stage Application Serial No. 10/533,555), WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789), and WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004), each of which is incorporated herein by reference for all purposes. In particular, the applications cited in this paragraph are incorporated for the purpose of providing specific examples and generic embodiments (and the definitions associated with the terms used in the embodiments) of compounds

that are useful in the practice of the invention. These references also describe in vitro assays useful in the practice of this invention.

[00110] "Taxane(s)" includes, for example, one or more of the following: Paclitaxel (Taxol®) and Docetaxel (Taxotere®).

[00111] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[00112] "Topoisomerase inhibitor" includes, for example, one or more of the following: amsacrine, camptothecin, etoposide, etoposide phosphate, exatecan, irinotecan, lurtotecan, and teniposide, and topotecan.

[00113] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[00114] "SRC and/or ABL kinase inhibitor(s)" includes, for example, dasatinib, imatinib (Gleevec®), and compounds described in WO 2006/074057.

[00115] "VEGFR inhibitor" includes, for example, one or more of the following: ZD6474 (Zactima), sorafenib, Angiozyme, AZD2171, SU5416, PTK787, AEE788, sunitinib (SUTENT), and compounds described in WO 2004/050681 and WO 2004/006846.

Embodiments of the Invention

[00116] In one embodiment, the cancer is mediated, at least in part, by inhibiting MEK.

[00117] In another embodiment, the cancer is selected from melanoma, colon cancer, rectal cancer, pancreatic cancer, breast cancer, non-small cell lung cancer, small cell lung cancer, papillary thyroid cancer, anaplastic thyroid cancer, endometrial cancer, and ovarian cancer.

[00118] In another embodiment, one or more of the treatment(s) is one or more chemotherapeutic agent(s).

[00119] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from a taxane(s), a platin(s), a topoisomerase inhibitor(s), an alkylating agent(s), an antimetabolite(s), an antimicrotubule agent(s), and a bcr-abl inhibitor(s). In another embodiment, one or more of the chemotherapeutic agent(s) is an antimicrotubule agent(s) selected from Vincristine,Vinblastine, Vinorelbine, and Vindesine.

[00120] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from rapamycin, carboplatin, cisplatin, oxaliplatin, gemcitabine, dacarbazine, topotecan, and irinotecan.

[00121] In another embodiment, one or more of the chemotherapeutic agent(s) is an AKT inhibitor. In another embodiment, the AKT inhibitor is selected from a compound in Table 2a and Table 2b.

[00122] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from a compound in Table 2a and Table 2b.

[00123] In another embodiment, one or more of the chemotherapeutic agent(s) is a cMET inhibitor. In another embodiment, the cMET inhibitor is selected from a compound in Table 3a, Table 3b, and Table 3c.

[00124] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from a compound in Table 3a, Table 3b, and Table 3c.

[00125] In another embodiment, one or more of the chemotherapeutic agent(s) is an EGFR inhibitor. In another embodiment, the EGFR inhibitor is selected from Lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788, HKI-272, EKB-569, CI1033, and a compound selected from Table 4 and

Table 7. In another embodiment, the EGFR inhibitor is selected from Table 4 and Table 7.

[00126] In another embodiment, one or more of the chemotherapeutic agent(s) is a compound selected from Table 4 and Table 7.

[00127] In another embodiment, one or more of the chemotherapeutic agent(s) is an ErbB2 inhibitor. In another embodiment, the chemotherapeutic agent(s) is selected from lapatinib, EKB-569, HKI272, and CI1033.

[00128] In another embodiment, one or more of the chemotherapeutic agent(s) is an HSP90 inhibitor. In another embodiment, the HSP90 inhibitor is 17-AAG, 17-DMAG, Geldanamycin, and CNF2024.

[00129] In another embodiment, one or more of the chemotherapeutic agent(s) is an IGF1R inhibitor. In another embodiment, the IGF1R inhibitor is selected from a compound in Table 5a and Table 5b.

[00130] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from a compound in Table 5a and Table 5b.

[00131] In another embodiment, one or more of the chemotherapeutic agent(s) is an Raf inhibitor. In another embodiment, the Raf inhibitor is selected from sorafenib and a compound in Table 6.

[00132] In another embodiment, one or more of the chemotherapeutic agent(s) is a VEGFR inhibitor. In another embodiment, the VEGFR inhibitor is selected from a compound in Table 4 and Table 7.

[00133] In another embodiment, one or more of the chemotherapeutic agent(s) is selected from rapamycin, a rapamycin analogue, PI103, SF1126, and BEZ235. In another embodiment, one or more of the chemotherapeutic agent(s) is selected from rapamycin, CCI-779, AP23573, RAD001, TAFA93, PI103, SF1126, and BEZ235. In another embodiment, one or more of the chemotherapeutic agent(s) is selected from rapamycin, CCI-779, AP23573, RAD001, PI103, and SF1126. In another embodiment, one or more of the chemotherapeutic agent(s) is rapamycin. In another embodiment, one or more of the chemotherapeutic agent(s) is a rapamycin analogue.

[00134] In another embodiment, one or more of the chemotherapeutic agent(s) is 2-methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)phenyl)propanenitrile.

[00135] In another embodiment, one or more of the treatment(s) is selected from radiation and hypothermia therapy. In another embodiment, one or more of the treatment(s) is radiation.

[00136] In another embodiment, one or more of the treatment(s) is one or more antibody(s). In another embodiment, one or more of the antibody(s) is selected from IGF1R antibody (including, for example, αIGF-1R A12 MoAb, 19D12, h7C10 and CP-751871), Alemtuzumab, Bevacizumab (Avastin®), Cetuximab (Erbitux®), Gemtuzumab, Gemtuzumab ozogamicin, Ibritumomab (tiuxetan), Panitumumab, Rituximab, Tositumomab, and Trastuzumab (Herceptin®).

[00137] In another embodiment, one or more of the treatment(s) is surgery.

[00138] In another embodiment, one or more of the treatment(s) is one or more hormone therapy(s). In another embodiment, one or more of the hormone therapy(s) is selected from tamoxifen and an aromatase inhibitor.

[00139] In another embodiment, one or more of the chemotherapeutic agent(s) is gemcitabine.

[00140] In another embodiment, one or more of the chemotherapeutic agent(s) is Imatinib (i.e. Gleevec®).

[00141] In another embodiment, the cancer is primary or relapsed CML and/or acute myelogenous leukemia (AML) and one or more of the treatment(s) is selected from one or more of the chemotherapeutic agent(s) and one or more antibody(s). In another embodiment one or more of the chemotherapeutic agent(s) is selected from Imatinib (i.e. Gleevec®) and PKC412; in another embodiment, one or more of the chemotherapeutic agent(s) is Imatinib (i.e. Gleevec®). In another embodiment one or more of the antibody(s) is selected from αIGF-1R A12 MoAb and trastuzumab.

[00142] In another embodiment, the cancer is prostate cancer and one or more of the treatment(s) is selected from one or more antibody(s). In another embodiment one or more of the antibody(s) is αIGF-1R A12 MoAb.

[00143] In another embodiment, the cancer is malignant melanoma and one or more of the treatment(s) is selected from surgery and one or more chemotherapeutic agent(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from an alkylating agent(s), a taxane(s), a platin(s), and a Raf inhibitor(s). In another embodiment, one or more chemotherapeutic agent(s) is selected from sorafenib, Paclitaxel (Taxol®), Docetaxel (Taxotere®), dacarbazine, rapamycin, imatinib mesylate (Gleevec®), sorafenib, and carboplatin.

[00144] In another embodiment, the cancer is colon or rectal cancer and one or more of the treatment(s) is selected from surgery, radiation, one or more chemotherapeutic agent(s), and one or more antibody(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from cisplatin, oxaliplatin, carboplatin, 5-fluorouracil, Capecitabine (Xeloda), Irinotecan (Camptosar), FOLFOX (Folinic acid, 5-FU, Oxaliplatin), and leucovorin. In another embodiment one or more of the antibody(s) is selected from bevacizumab and cetuximab.

[00145] In another embodiment, the cancer is pancreatic cancer and one or more of the treatment(s) is selected from surgery, radiation, and one or more chemotherapeutic agent(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from erlotinib (Tarceva®), gemcitabine, 5-fluorouracil, leucovorin, cisplatin, oxaliplatin, carboplatin, gemcitabine, irinotecan, paclitaxel, capecitabine, and streptozocin.

[00146] In another embodiment, the cancer is breast cancer and one or more of the treatment(s) is selected from surgery, radiation, one or more chemotherapeutic agent(s), one or more hormone therapy(s), and one or more antibody(s). In another embodiment one or more of the chemotherapeutic agent(s) is selected from lapatinib (Tykerb®), Paclitaxel (Taxol®), docetaxel, capecitabine, Cyclophosphamide (Cytoxan), methotrexate, fluorouracil, doxorubicin, epirubicin, gemcitabine, carboplatin (Paraplatin), cisplatin (Platinol), vinorelbine (Navelbine), capecitabine (Xeloda), pegylated liposomal doxorubicin (Doxil), and albumin-bound paclitaxel (Abraxane). In another embodiment one or more of the antibody(s) is selected from α IGF-1R A12 MoAb, bevacizumab (Avastin), and trastuzumab. In another embodiment, one or more of the hormone therapy(s) is selected from tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, and an aromatase inhibitor(s); in another embodiment, one or more of the aromatase inhibitor(s) is selected from etrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin).

[00147] In another embodiment, the cancer is non-small cell lung cancer and one or more of the treatment(s) is selected from surgery, radiation, one or more antibody(s), and one or more chemotherapeutic agent(s). In another embodiment, the chemotherapeutic agent(s) is selected from cisplatin, oxaliplatin, carboplatin, Zactima (ZD6474), Paclitaxel, Docetaxel (Taxotere®), Gemcitabine (Gemzar®), Vinorelbine,

Irinotecan, Etoposide, Vinblastine, Erlotinib (Tarceva®), and Pemetrexed. In another embodiment, one or more of the antibody(s) is Bevacizumab.

[00148] In another embodiment, the cancer is small cell lung cancer and one or more of the treatment(s) is selected from surgery, radiation, and one or more chemotherapy agent(s). In another embodiment, one or more of the chemotherapy agent(s) is selected from cisplatin, oxaliplatin, carboplatin, etoposide, irinotecan, fosfamide, paclitaxel, docetaxel, gemcitabine, Topotecan, cyclophosphamide/doxorubicin/vincristine (CAV), methotrexate, and vinorelbine.

[00149] In another embodiment, the cancer is papillary or anaplastic thyroid cancer, and one or more of the treatment(s) is selected from surgery, radiation, radioactive iodine therapy, one or more hormone therapy(s), and one or more chemotherapeutic agent(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from thyroid hormone pills, Doxorubucin and a platin(s).

[00150] In another embodiment, the cancer is endometrial cancer and one or more of the treatment(s) is selected from surgery, radiation, hormone therapy, and one or more chemotherapeutic agent(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from paclitaxel, doxorubicin, and cisplatin. In another embodiment, one or more of the hormone therapy is selected from medroxyprogesterone acetate, megestrol acetate, and Tamoxifen.

[00151] In another embodiment, the cancer is ovarian cancer and one or more of the treatment(s) is selected from surgery, radiation, and one or more chemotherapeutic agent(s). In another embodiment, one or more of the chemotherapeutic agent(s) is selected from a platin(s) compound (such as cisplatin, oxaliplatin and carboplatin), a taxane (such as paclitaxel or docetaxel), topotecan, anthracyclines (such as doxorubicin (Adriamycin) and liposomal doxorubicin (Doxil)), gemcitabine, cyclophosphamide, vinorelbine (Navelbine), hexamethylmelamine, ifosfamide, and etoposide.

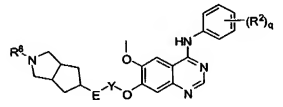
[00152] In another embodiment, one or more of the treatment(s) is selected from one or more chemotherapeutic agent(s), radiation, hypothermia therapy, one or more antibody(s), and surgery. In another embodiment, one or more of the chemotherapeutic agent(s) is selected from an EGFR inhibitor, isotretinoin, a platin (e.g., cisplatin, oxaliplatin, and carboplatin), epirubicin, bleomycin, doxorubicin, cyclophosphamide, a taxane (e.g. docetaxel (Taxotere®)), and fluorouracil [5-FU]. In

another embodiment, one or more of the chemotherapeutic agent(s) is selected from cisplatin, carboplatin, and docetaxel. In another embodiment, one or more of the antibody(s) is cetuximab (Erbitux®).

[00153] In another embodiment one or more of the treatment(s) is selected from radiation and surgery.

[00154] In another embodiment of the invention, one or more of the treatments is selected from rapamycin, CCI-779, AP23573, RAD001, carboplatin, cisplatin, oxaliplatin, gemcitabine, dacarbazine, topotecan, irinotecan, sorafenib, paclitaxel, docetaxel, Lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), 5-fluorouracil, Capecitabine (Xeloda), FOLFOX (Folinic acid, 5-FU, Oxaliplatin), streptozocin, Cyclophosphamide (Cytoxan), methotrexate, doxorubicin, epirubicin, vinorelbine (Navelbine), pegylated liposomal doxorubicin (Doxil), and albumin-bound paclitaxel (Abraxane), Etoposide, Vinblastine, Pemetrexed, leucovorin, fosfamide, cyclophosphamide/doxorubicin/vincristine (CAV), thyroid hormone pills, hexamethylmelamine, ifosfamide, Imatinib (i.e. Gleevec®), ^{a}IGF-1R A12 MoAb, IGF-1R 19D12, IGF-1R h7C10, IGF-1R CP-751871, Alemtuzumab, Bevacizumab (Avastin®), Cetuximab (Erbitux®), Gemtuzumab, Gemtuzumab ozogamicin, Ibritumomab (tiuxetan), Panitumumab, Rituximab, Tositumomab, Trastuzumab (Herceptin®), tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, medroxyprogesterone acetate, megestrol acetate, and an aromatase inhibitor.

[00155] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **100**:

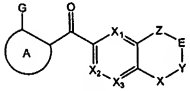


100

where q is 1, 2, or 3; E is $-NR^9-$, -O-, or absent and Y is $-CH_2CH_2-$, $-CH_2-$, or absent provided that when E is $-NR^9-$ or -O-, then Y is $-CH_2CH_2-$; R^2 is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-OR^3$, and optionally substituted lower alkyl; R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)N(R^3)R^4$, $-SO_2R^4$, and $-C(O)R^3$; or a single geometric isomer, stereoisomer, racemate, enantiomer, or

diastereomer, thereof and optionally as a pharmaceutically acceptable salt or hydrate thereof. The terms used to describe the scope of formula 100 are defined in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004) which is herein incorporated by reference. For example "optionally substituted alkyl" for formula 100 has the meaning given in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004). Whenever a compound of formula 100 is described in this application, whether by structure or by use of the term "formula 100," the terms used to describe that compound are defined by WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004).

[00156] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **101**:



101

or a pharmaceutically acceptable salt, hydrate or solvate thereof, where

A is a three- to seven-membered alicyclic, a five- to six-membered ortho-arylene or a five- to six-membered ortho-heteroarylene containing between one and three heteroatoms, either of the aforementioned optionally substituted with up to four R;

each R is independently selected from -H, halogen, -CN, $-NO_2$, $-OR^3$, $-N(R^3)R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2N(R^3)R^3$, $-CO_2R^3$, $-C(O)N(R^3)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, $-OC(O)R^3$, optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1\text{-}6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1\text{-}6}$alkyl;

optionally two of R, together with the atoms to which they are attached, form a first ring system fused with A, said first ring system substituted with zero to three of R^1;

X_1, X_2 and X_3 are independently selected from $-CR^1=$ or $-N=$;

each R^1 is independently selected from -H, halogen, -CN, $-NO_2$, $-OR^3$, $-N(R^3)R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2N(R^3)R^3$, $-CO_2R^3$, $-C(O)N(R^3)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, $-OC(O)R^3$, optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1\text{-}6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1\text{-}6}$alkyl;

Z and X are each independently selected from $-C(R^2)=$, $-N=$, $-N(R^2)-$, $-S(O)_{0-2}-$, and $-O-$;

E and Y are each independently selected from absent, $-C(R^2)(R^2)-$, $-C(=O)-$, $-C(R^2)=$ and $-N=$, but E and Y are not both absent, and E and Y are not both $-N=$ when both Z and X are $-N=$;

each R^2 is independently selected from R^3, $-N(R^3)(R^3)$, $-C(O)N(R^3)R^3$, $-N(R^3)CO_2R^3$, $-N(R^3)C(O)N(R^3)R^3$, and $-N(R^3)C(O)R^3$;

each R^3 is independently selected from -H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}alicyclic, optionally substituted aryl, optionally substituted aryl C_{1-3}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-3}alkyl;

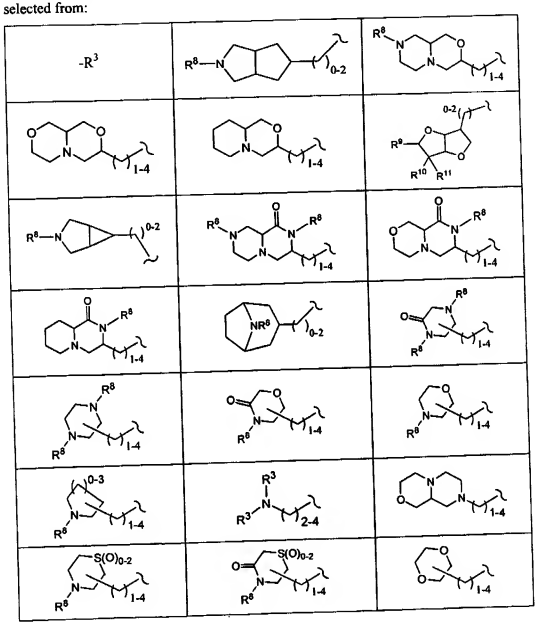
optionally two of R^3, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional heteroatom selected from N, O, S, and P; and

G is selected from $-CO_2R^3$, $-C(O)R^3$, $-C(O)N(R^3)R^3$, $-C(O)(NR^3)$, $-C(O)NR^3[C(R^3)_2]_{0-1}R^3$, $-C(O)NR^3O[C(R^3)_2]_{0-1}R^3$, $-N(R^3)CO_2R^3$, $-N(R^3)C(O)N(R^3)R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-SO_2N(R^3)R^3$, optionally substituted aryl C_{0-3}alkyl, and optionally substituted heterocyclyl C_{0-3}alkyl;

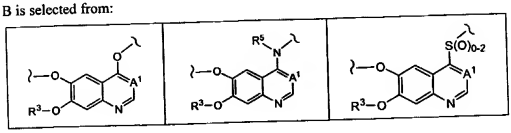
with the proviso, however, that the compound is not 2-[(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-6-yl)carbonyl]-*N*-(2-furanylmethyl)-benzamide, *N*-cyclopropyl-2-[(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-6-yl)carbonyl]-benzamide, or 2-[(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-6-yl)carbonyl]-*N*-(phenylmethyl)-benzamide.

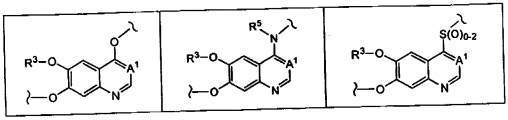
The terms used to describe the scope of formula 101 are defined in WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 101 has the meaning given in WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789). Whenever a compound of formula 101 is described in this application, whether by structure or by use of the term "formula 101," the terms used to describe that compound are defined by WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789).

[00157] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **A-B-C** or a pharmaceutically acceptable salt or hydrate thereof, wherein, A is selected from:

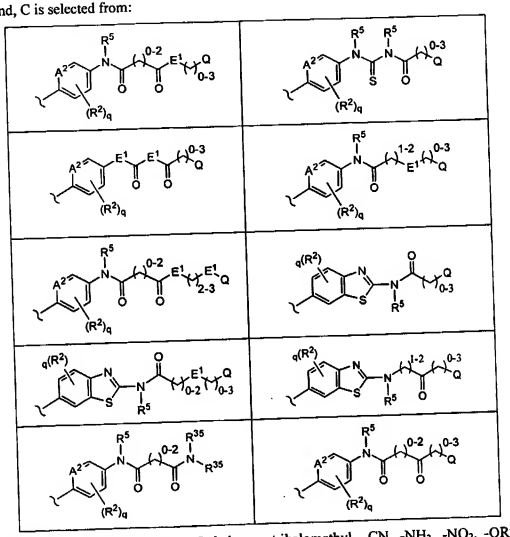


B is selected from:





and, C is selected from:



wherein R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 2;

each R^3 is independently selected from –H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

each R^{35} is independently selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl;

two R^{35}, together with the nitrogen to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic may have an additional annular heteroatom, and said heteroalicyclic may have an aryl fused thereto, said aryl optionally substituted with an additional one to four of R^{60};

A^1 is selected from =N-, =C(H)-, and =C(CN)-;

A^2 is either =N- or =C(H)-;

R^5 is -H or optionally substituted lower alkyl;

R^8 is selected from R^3, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo; and

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11};

E^1 is selected from -O-, $-CH_2-$, $-N(R^5)-$, and $-S(O)_{0-2}-$;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

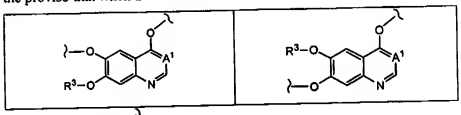
R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

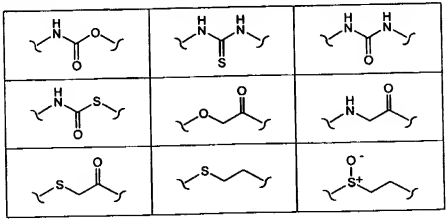
each methylene in any of the above formulae is independently optionally substituted with R^{25};

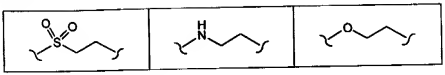
each R^{25} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0\text{-}2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of R^{25} on a single carbon can be oxo;

with the proviso that when B is selected from:

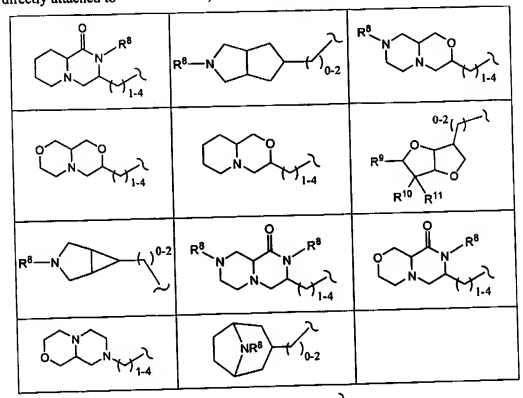


and C contains $(R^2)_q$, and the remaining portion of C contains one of:

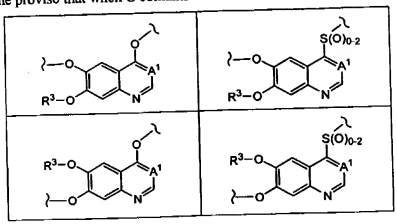


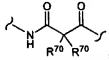


directly attached to $(R^2)_q$, then A must be one of:



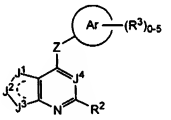
and with the proviso that when C contains $(R^2)_q$, and B is selected from:



then the portion of C directly attached to  cannot contain  , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

The terms used to describe the scope of formula A-B-C are defined in WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula A-B-C has the meaning given in WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336). Whenever a compound of formula A-B-C is described in this application, whether by structure or by use of the term "formula A-B-C," the terms used to describe that compound are defined by WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336).

[00158] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **103**:



103

or a pharmaceutically acceptable salt or hydrate hereof, wherein,

each of J^1, J^2, and J^3 is independently selected from =N-, =C(R^1)-, -N(R^1)-, -O- and -S(O)$_{0-2}$-;

each R^1 is independently selected from -H, halogen, trihalomethyl, -CN, -NO_2, -OR^{20}, -N(R^{20})R^{20}, -S(O)$_{0-2}R^{20}$, -SO_2N(R^{20})R^{20}, -CO_2R^{20}, -C(O)N(R^{20})R^{20}, -N(R^{20})SO_2R^{20}, -N(R^{20})C(O)R^{20}, -NCO_2R^{20}, -C(O)R^{20}, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl and -D-R^{50};

R^2 is selected from -H, halogen, -OR^{20}, -S(O)$_{0-2}R^{20}$, -NO_2, -N(R^{20})R^{20}, and optionally substituted C_{1-6}alkyl;

J^4 is selected from =N-, =C(H)-, and =C(CN)-;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

each R^3 is independently selected from -H, halogen, trihalomethyl, -CN, -NO_2, -OR^{20}, -$N(R^{20})R^{20}$, -$S(O)_{0-2}R^{20}$, -$SO_2N(R^{20})R^{20}$, -CO_2R^{20}, -$C(O)N(R^{20})R^{20}$, -$N(R^{20})SO_2R^{20}$, -$N(R^{20})C(O)R^{20}$, -NCO_2R^{20}, -$C(O)R^{20}$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl and a group -B-L-T, wherein

B is selected from absent, -$N(R^{13})$-, -$N(SO_2R^{13})$-, -O-, -$S(O)_{0-2}$-, and -C(=O)-;

L is selected from absent, -C(=S)$N(R^{13})$-, -C(=NR^{14})$N(R^{13})$-, -$SO_2N(R^{13})$-, -SO_2-, -C(=O)$N(R^{13})$-, -$N(R^{13})$-, -C(=O)C_{1-2}alkyl$N(R^{13})$ -, -$N(R^{13})C_{1-2}$alkylC(=O)-, -C(=O)C_{0-1}alkylC(=O)$N(R^{13})$-, -C_{0-4}alkylene-, -C(=O)C_{0-1}alkylC(=O)OR^3-, -C(=NR^{14})C_{0-1}alkylC(=O)-, -C(=O)-, -C(=O)C_{0-1}alkylC(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, -R^{13}, -C_{0-4}alkyl, -C_{0-4}alkylQ, -OC_{0-4}alkylQ, -C_{0-4}alkylOQ, -$N(R^{13})C_{0-4}$alkylQ, -SO_2C_{0-4}alkylQ, -C(=O)C_{0-4}alkylQ, -C_{0-4}alkyl$N(R^{13})$Q, and -C(=O)$N(R^{13})C_{0-4}$alkylQ,

wherein each of the aforementioned alkyls and alkylenes of -B-L-T is optionally substituted with one or two of R^{60};

Z is selected from -$S(O)_{0-2}$-, -O-, and -NR^4-;

R^4 is either -H or optionally substituted C_{1-6}alkyl;

each D is independently selected from -O-, -$S(O)_{0-2}$-, and -NR^5-;

each R^5 is independently -H or optionally substituted C_{1-6}alkyl;

each R^{13} is independently selected from -H, -C(=O)R^{20}, -C(=O)OR^{20}, -C(=O)SR^{20}, -SO_2R^{20}, -C(=O)$N(R^{20})R^{20}$, and optionally substituted C_{1-4}alkyl;

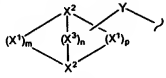
two of R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic can comprise up to four annular heteroatoms, and said heteroalicyclic can comprise an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

each R^{14} is independently selected from -H, -NO_2, -$N(R^{20})R^{20}$, -CN, -OR^{20}, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-}

$_{6}$alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl;

Q is a five- to ten-membered annular system, optionally substituted with between zero and four of R^{20};

each R^{50} is independently either R^{20}, or according to formula **120**;



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wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-OR^{20}$, $-N(R^{20})R^{20}$, $-S(O)_{0-2}R^{20}$, $-SO_2N(R^{20})R^{20}$, $-CO_2R^{20}$, $-C(O)N(R^{20})R^{20}$, $-N(R^{20})SO_2R^{20}$, $-N(R^{20})C(O)R^{20}$, $-NCO_2R^{20}$, $-C(O)R^{20}$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl,

optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

each R^8 is independently selected from $-R^{20}$, Y, $-SO_2N(R^{20})R^{20}$, $-CO_2R^{20}$, $-C(O)N(R^{20})R^{20}$, $-SO_2R^{20}$, and $-C(O)R^{20}$;

each R^{20} is independently selected from -H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl; or two of R^{20}, when taken together with a common nitrogen to which they are attached, can form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

each R^{60} is independantly selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-OR^{20}$, $-N(R^{20})R^{20}$, $-S(O)_{0-2}R^{20}$, $-SO_2N(R^{20})R^{20}$, $-CO_2R^{20}$, $-C(O)N(R^{20})R^{20}$, $-N(R^{20})SO_2R^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})CO_2R^{20}$, $-C(O)R^{20}$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl;

two of R^{60}, when taken together with a common carbon to which they are attached, can form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; and

two of R^{60}, when taken together can be oxo.

The terms used to describe the scope of formula 103 are defined in WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 103 has the meaning given in WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140). Whenever a compound of formula 103 is described in this application, whether by structure or by use of the term "formula 103," the terms used to describe that compound are defined by WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140).

[00159] In another embodiment, one or more of the chemotherapeutic agent(s) is *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-[2-(4-fluorophenyl)ethyl]ethanediamide or pharmaceutically acceptable salt or hydrate thereof.

[00160] In another embodiment, the cMet inhibitor is *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-[2-(4-fluorophenyl)ethyl]ethanediamide or a pharmaceutically acceptable salt or hydrate thereof.

[00161] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **105**:

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or a pharmaceutically acceptable salt or hydrate thereof, wherein,

V is NR_1R_{1a}, or O-R_1, wherein

R_1 is H, CN, halo, $-NR_{13}R_{14}$, $C(O)NR_{13}R_{14}$, C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, -C_0-C_6 alkyl-R_{20}, wherein R_{20} is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclical or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, C_3-C_7 heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from C_1-C_6 alkyl, and -C_0-C_6 alkyl-R_{21};

R_{1a} is H or C_1-C_6 alkyl; or

when V is NR_1R_{1a}, R_1 and R_{1a} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing, in addition to the nitrogen, up to two additional heteroatoms independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of C_1-C_6 alkyl, $-NR_{13}R_{14}$ or C_3-C_7 cycloalkyl;

X is H, halo, C_1-C_6 alkyl, NO_2, mono-, di-, or tri-halo substituted methyl, $NR_{13}R_{14}$, C(O)O-C_1-C_6 alkyl, or N(R_{13})-C(O)-C_1-C_6 alkyl;

Y is H, halo, OH, C_1-C_6 alkyl, C_0-C_6 alkyl-$NR_{15}R_{16}$, $NR_{15}R_{16}$, C_1-C_6 alkoxy, -$N(R_{13})$-$(CH_2)_n$-$NR_{15}R_{16}$, -C(O)O-C_1-C_6 alkyl, -O-$(CH_2)_n$-$NR_{15}R_{16}$, -C(O)-C_1-C_6 alkyl, -C_0-C_6-alkyl-R_{21}, -O-R_{21}, -C(O)-R_{21}, -O-$(CH_2)_n$-R_{21}, -C(O)-$NR_{13}R_{14}$, -C(O)-$N(R_{13})$-aryl, -C(O)-$N(R_{13})$-$(CH_2)_n$-$NR_{15}R_{16}$, -C(O)-$N(R_{13})$-$(CH_2)_n$-aryl, -C(O)-$N(R_{13})$-$(CH_2)_n$-heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C_1-C_6 alkyl, aryl-C_1-C_6 alkyl-, aryl-$(CH_2)_n$-O-$(CH_2)_n$-aryl-, arylOH, C_3-C_7 cycloalkyl, heterocyclyl, -aryl-$N(R_{13})C(O)$-C_3-C_7 cycloalkyl-C(O)-$N(R_{14})$-aryl, or a group of the formula -L-M-Q, wherein

L is a bond or C_3-C_7 cycloalkyl,

M is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl,

Q is $NR_{13}R_{14}$, $N(R_{13})C(O)$-C_1-C_6 alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, C(O)O-$(CH_2)_n$-phenyl, and C(O)-C_1-C_6 alkyl;

Z is H, NR_2R_3, -S-R_{2a}, or -O-R_{2a}, wherein

R_2 is -C_1-C_6 alkyl, -C_1-C_6 alkyl-$NR_{13}R_{14}$, -C(O)-aryl, -C_0-C_6-alkyl-aryl, -C_0-C_6-alkyl-heteroaryl, -C_0-C_6-alkyl-(C_3-C_7-cycloalkyl), -C_0-C_6-alkyl-heterocyclyl, or -C_0-C_6 alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein

each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, C_3-C_7 cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO_2, $NR_{13}R_{14}$, C(O)O-C_1-C_6 alkyl, $N(R_{13})C(O)$-C_1-C_6 alkyl, -$SO_2NR_{13}R_{14}$, -O-C(O)-$NR_{13}R_{14}$, -C_0-C_6 alkyl-$C(O)NR_{15}R_{16}$, C_1-C_6 alkoxy, C_1-C_6

thioalkoxy, -O-$(CH_2)_n$-$NR_{15}R_{16}$, -C_1-C_6 alkyl-$NR_{13}R_{14}$, -$N(R_{13})$-C(O)-C_1-C_6 alkyl, -$N(R_{13})$-C(O)-aryl, -C_0-C_6 alkyl-$C(O)N(R_{13})$-$(CH_2)_n$-$NR_{15}R_{16}$, -C_0-C_6 alkyl-C(O)-$N(R_{13})$-$(CH_2)_n$-aryl, -O-$(CH_2)_n$-C(O)-$N(R_{13})$-$(CH_2)_n$-$NR_{15}R_{16}$, -O-$(CH_2)_n$-C(O)-$NR_{15}R_{16}$, -C_0-C_6 alkyl-C(O)-$N(R_{13})$-$(CH_2)_n$-O-C_1-C_6 alkyl, -C_0-C_6 alkyl-$N(R_{13})$-C(O)O-C_1-C_6 alkyl, -C_0-C_6alkyl-C(O)-heterocyclyl, -C_0-C_6alkyl-C(O)-heteroaryl, -C_0-C_6alkyl-C(O)-aryl, -C_0-C_6-alkyl-R_{21}, aryloxy, -O-$(CH_2)_n$-R_{21}, -SO_2-heterocyclyl, $N(R_{13})$-C(O)-C_3-C_7-cycloalkyl, -C_0-C_6alkyl C(O)O-R_{21} ,C_3-C_7-cycloalkyl, -C_0-C_6alkylR_{21}, -SC_1-C_6alkyl or C_1-C_6 alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, CF_3, C_1-C_6 alkyl, C_1-C_6 haloalkoxy, $NR_{13}R_{14}$ and C_1-C_6 alkoxy;

R_3 is H or C_1-C_6 alkyl;

or R_2 and R_3 together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing up to three heteroatoms independently selected from O, N, and S, and wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two of halo or C_1-C_6 alkyl;

R_{2a} is aryl or C_0-C_6 alkyl-heteroaryl, wherein the aryl and heteroaryl are optionally substituted with aryl, -$N(R_{13})$-C(O)-C_3-C_7 cycloalkyl or -C(O)$NR_{13}R_{14}$;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl;

R_{15} and R_{16} are independently H, C_1-C_6 alkyl, heteroaryl, or heterocyclyl, or R_{15} and R_{16} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C_1-C_6 alkyl, or -C(O)O-C_1-C_6 alkyl;

R_{21} is heterocyclyl, aryl, heteroaryl, or C_3-C_7 cycloalkyl, and wherein alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, and heterocyclyl are optionally substituted with

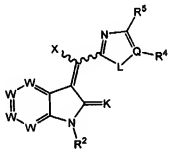
one or two moieties independently selected from halo, $-S(O)_2-C_0-C_1$ alkyl, $-C(O)-C_0-C_1$ alkyl, $-C(O)-H$, $-C_0-C_1$ alkyl-aryl, C_1-C_6 alkyl, $NR_{13}R_{14}$, and heterocyclyl;

n is 0-6;

provided that when V is NH_2, X, Y and Z are not simultaneously H.

The terms used to describe the scope of formula 105 are defined in WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719) which is herein incorporated by reference. For example "optionally substituted heterocyclyl" for formula 105 has the meaning given in WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719). Whenever a compound of formula 105 is described in this application, whether by structure or by use of the term "formula 105," the terms used to describe that compound are defined by WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719).

[00162] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **107**:



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or a pharmaceutically acceptable salt or hydrate thereof, wherein,

each W is independently N or CR^1;

each R^1 is independently selected from -H, halogen, trihaloalkyl, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-N{=}CNR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^7$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, $-R^7$, and $-A-R^7$; provided at least one of R^1 is $-A-R^7$, wherein, only for said at least one $-A-R^7$, R^7 must be an optionally substituted heteroalicyclic ring, and any nitrogen of said optionally substituted heteroalicyclic ring cannot be directly bound to A;

A is O, $S(O)_{0-2}$, and NR^6;

L is O, $S(O)_{0-2}$, or NR^3;

Q is C or N, when Q is N, then R^4 does not exist;

R^2 and R^3 are each independently -H or $-R^7$;

R^4 and R^5 are each independently selected from -H, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, -CN, $-NO_2$, $-NH_2$, halogen, trihalomethyl, and $-R^7$; or

R^4 and R^5, when taken together, form a five or six-membered aromatic ring system containing between zero and two nitrogens, said five or six-membered aromatic ring system optionally substituted with between zero and four of R^{15};

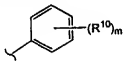
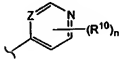
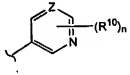
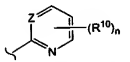
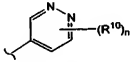
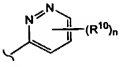
R^6 is selected from -H, optionally substituted C_{1-8}alkyl, optionally substituted arylC_{1-8}alkyl, optionally substituted heterocyclylC_{1-8}alkyl, optionally substituted aryl, and optionally substituted heterocyclyl;

R^7 is selected from -H, optionally substituted C_{1-8}alkyl, optionally substituted arylC_{1-8}alkyl, optionally substituted heterocyclylC_{1-8}alkyl, optionally substituted aryl, and optionally substituted heterocyclyl; provided that there are at least two carbons between any heteroatom of R^7 and A or either nitrogen to which R^2 or R^3 are attached; or

R^6 and R^7, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclic ring, said optionally substituted five- to seven-membered heterocyclic ring optionally containing at least one additional heteroatom selected from nitrogen, oxygen, sulfur, and phosphorus;

R^8 is -H, $-NO_2$, -CN, $-OR^6$, and optionally substituted C_{1-8}alkyl;

X is selected from one of the following six formulae:

wherein m is zero to five, n is zero to three, and Z is N or CR^{10};

R^{10} is selected from -H, halogen, trihalomethyl, $-NH_2$, $-NO_2$, $-OR^6$, $-N{=}CNR^6R^7$, $-NR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, and R^7;

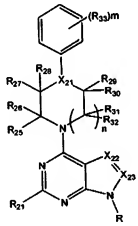
K is O, S, or NR^{11};

R^{11} is selected from cyano, $-NO_2$, $-OR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(O)R^7$, and R^6; and

each R^{15} is independently selected from -H, halogen, $-NH_2$, $-NO_2$, $-OR^6$, $-N{=}CNR^6R^7$, $-NR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, and R^7.

The terms used to describe the scope of formula 107 are defined in WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555) which is herein incorporated by reference. For example "optionally substituted aryl" for formula 107 has the meaning given in WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555).Whenever a compound of formula 107 is described in this application, whether by structure or by use of the term "formula 107," the terms used to describe that compound are defined by WO 2004/050681 (US Nat'l Stage Application Serial No. 10/533,555).

[00163] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **108**:



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or a pharmaceutically acceptable salt or hydrate thereof, wherein,

X_{21} is N or CR_{22};

X_{22} is N or CR_{23};

X_{23} is N or CR_{24}, but when X_{22} is N then X_{23} is CR_{24};

each of R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29} and R_{30}, and each R_{31}, R_{32} and R_{33} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NR_{35}R_{35a}$,

$-S(O)_{0-2}R_{35}$, $-SO_2NR_{35}R_{35a}$, $-CO_2R_{35}$, $-C(O)NR_{35}R_{35a}$, $-N(R_{35})SO_2R_{35}$, $-N(R_{35})C(O)R_{35}$, $-N(R_{35})CO_2R_{35}$, $-OR_{35}$, $-C(O)R_{35}$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, and optionally substituted arylalkyl;

R is selected from -H, halogen, trihalomethyl, $-S(O)_{0-2}R_{35}$, $-SO_2NR_{35}R_{35a}$, $-CO_2R_{35}$, $-C(O)NR_{35}R_{35a}$, $-OR_{35}$, $-C(O)R_{35}$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, and optionally substituted arylalkyl; or

two of R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} or R_{32}, together with the atom or respective atoms to which they are attached, combine to form an optionally substituted spirocyclic ring system, optionally substituted fused ring system, and optionally substituted saturated bridged ring system;

each of R_{35} and R_{35a} is independently selected from -H, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted lower aryl alkoxy, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

R_{35} and R_{35a}, together with the atom or respective atoms to which they are attached, combine to form an optionally substituted five- to seven-membered heterocyclyl; and

m is an integer from 0 to 5;

n is an integer from 1 to 2; and

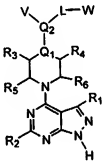
with the provisos that when X_{22} is CR_{23} and X_{23} is N then R is not optionally substituted aryl, aralkyl or heteroaryl, and that when X_{22} is N and X_{23} is CR_{24} then R is not optional substituted aryl or heteroaryl and R_{21} is not $-NR_{35}R_{35a}$, and that when X_{22} is CR_{23} and X_{23} is CR_{24} then R_{21} is not optionally substituted aryl;

and that compounds 4-(4-(2-fluorophenyl)piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine, 4-(4-(3-chlorophenyl)piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine, 6-(4-(2-nitro-4-(trifluoromethyl)phenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(4-fluorophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(2,5-dimethylphenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(3,4-dichlorophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(2-fluorophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(3-chlorophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(4-methoxyphenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(4-nitrophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-phenylpiperazin-

1-yl)-7*H*-purine, 4-(4-phenylpiperazin-1-yl)-7*H*-pyrrolo[2,3-d]pyrimidine, 4-phenyl-1-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-ol, 6-(4-(2-methoxyphenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(2-chlorophenyl)piperazin-1-yl)-7*H*-purine, 6-(4-o-tolylpiperazin-1-yl)-7*H*-purine, 6-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)-7*H*-purine, 6-(4-(2-methoxyphenyl)piperazin-1-yl)-7*H*-purine are not included in Formula I.

The terms used to describe the scope of formula 108 are defined in WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173) which is herein incorporated by reference. For example "optionally substituted aryl" for formula 108 has the meaning given in WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173). Whenever a compound of formula 108 is described in this application, whether by structure or by use of the term "formula 108," the terms used to describe that compound are defined by WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173).

[00164] In another embodiment, one or more of the chemotherapeutic agent(s) is of formula **109**:



109

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

R_1 is H, halo, cyano, aryl, heteroaryl, C_{1-4} alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the aryl, heteroaryl, alkyl, alkenyl and alkynyl are optionally substituted with one or two groups independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$;

R_2 is H, NH_2, SH, OH, or C_1-C_2 alkyl;

R_3, R_4, R_5, and R_6 are each independently H, oxo, CO_2R_{10}, $CONR_{10}R_{11}$, C_{1-4} alkyl, C_1-C_6 alkoxy, or C_1-C_6 alkoxy-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl, C_1-C_6 alkoxy and C_1-C_6 alkoxy-C_1-C_4 alkyl in each group are independently optionally substituted with

1 or 2 substituents independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$, or

R_3 and R_5 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino,

R_4 and R_6 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino R_3 and R_6 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino, or

R_4 and R_5 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino;

L is C_{0-4} alkyl, C_2-C_6 alkenyl, $-N(R_{12})-$, $-C(O)N(R_{12})-$, $-N(R_{12})C(O)-$, $-C(O)-$, $-O-(CH_2)_n-$, or $-(CH_2)_n-O-$, wherein n is 1-4;

Q_1 is N or CR_{13}, wherein R_{13} is H or $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$;

Q_2 is a bond, CR_{14}, O or N, wherein R_{14} is H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_{15}R_{15}$, wherein R_{15} is H or C_{1-4} alkyl, or Q_2 and V together form C(=O);

when Q_2 is a bond,

V is absent and R_{13} is not H;

when Q_1 is CR_{13} and Q_2 is CH,

V is H, OH, NH_2, C_1-C_6 alkoxy, $NR_{10}R_{11}$, $O(CH_2)_nNR_{10}R_{11}$, $O(CH_2)_n$ attached to a C or N of a 4-7 membered heterocyclyl, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered unsaturated cyclic containing 1-3 atom of O or N, or

V is a bicyclic solublizing group;

when Q_1 is N and Q_2 is CH, or when Q_1 is CR_{13} and Q_2 is O or N,

V is H, $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, C(O) $(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$,

$SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered saturated or unsaturated cyclic or heterocyclic containing 1-3 atoms of O or N, optionally substituted with 1 or 2 C_1-C_3 alkoxy groups or

V is a "bicyclic solublizing group";

m is 1-3,

n is 1-4,

W is C_1-C_6 alkyl, $NR_{10}R_{11}$, or W is

aryl, C_3-C_7 cycloalkyl, heterocyclyl, heteroaryl, or 5-12 membered fused bicylic or tricyclic saturated, partially saturated, or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each aryl, cycloalkyl, heterocyclyl, heteroaryl, and fused bicyclic or tricyclic ring system is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, C(O)OC_1-C_6 alkyl, C(O)NR_{12}-C_1-C_6 alkoxy, C(O)NR_{12}-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo, or

V, Q_2, L, and W together form an aryl ring, heteroaryl ring, C_3-C_7 cycloalkyl ring, heterocyclyl ring, or a 5-12 membered fused bicylic or tricyclic saturated, partially saturated or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each ring or ring system is optionally substituted with 1, 2, or 3 groups independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, C(O)OC_1-C_6 alkyl, C(O)NR_{12}-C_1-C_6 alkoxy, C(O)NR_{12}-heterocyclyl, aryl, O-aryl, NH-aryl, wherein each aryl substituent is optionally further substituted with halo; and

R_{10}, R_{11} and R_{12} are each independently H or $C_{1\text{-}6}$ alkyl which is optionally substituted with aryl or heteroaryl,

provided the compound is not a compound selected from:

4-(4-(2-fluorophenyl)piperazin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine;

4-(4-(3-chlorophenyl)piperazin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine;

ethyl 4-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate;

tert-butyl 4-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)piperazine-1-carboxylate; and

N-(4-phenoxyphenyl)-4-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxamide.

The terms used to describe the scope of formula 109 are defined in WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291 which is herein incorporated by reference. For example "optionally substituted aryl" for formula 109 has the meaning given in WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291. Whenever a compound of formula 109 is described in this application, whether by structure or by use of the term "formula 109," the terms used to describe that compound are defined by WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291.

[00165] . For each of the foregoing embodiments, the Compound of Formula I can be selected from any of the following embodiments, including from the Representative Compounds in Table 1.

[00166] In another embodiment of the Invention, the Compound of Formula I is that where R^7 is halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. In another embodiment, R^7 is iodo or bromo. In another embodiment, R^7 is iodo. In another embodiment, the compound is that where R^7 is iodo or bromo and all other groups are as defined in the Summary of the Invention for Group A.

[00167] In another embodiment of the Invention, the Compound of Formula I is that where X is halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. In another embodiment, X is fluoro or chloro. In another embodiment, X is fluoro. In another embodiment, the compound is that where X is fluoro or chloro and all other groups are as defined in the Summary of the Invention for Group A.

[00168] In another embodiment of the Invention, the Compound of Formula I is that where R^7 and X are halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. More specifcally, R^7 is iodo and X is fluoro. In another embodiment, the compound is that where R^7 is iodo and X is fluoro and all other groups are as defined in the Summary of the Invention for Group A.

[00169] In another embodiment of the Invention, the Compound of Formula I is that where R^1, R^2, R^5, and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. In another embodiment, R^1, R^2, R^5, and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A.

[00170] In another embodiment of the Invention, the compound of Formula I is selected from Group A where all groups are as defined in the Summary of the Invention.

[00171] In another embodiment of the invention (A1), the Compound of Formula I is that where X and R^7 are halo and all other groups are as defined in the Summary of the Invention for a compound of Group A.

[00172] In another embodiment (A2), the compound of Formula I is selected from Group A where R^{10} and R^{12} are independently hydrogen or halo. In another embodiment, R^{10} and R^{12} are independently hydrogen or fluoro. In another embodiment, R^{10} is 3-fluoro and R^{12} is hydrogen. In another embodiment, R^{10} and R^{12} are fluoro, in another embodiment, 3-fluoro and 4-fluoro, 4-fluoro and 5-fluoro, or 4-fluoro and 6-fluoro.

[00173] In another embodiment of the invention (A3), the compound of Formula I is that where R^1, R^2, R^5 and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A.

[00174] In another embodiment (A4), the compound of Formula I is selected from Group A where X, R^7, and A are as defined in the Summary of the Invention; and one of R^1, R^2, R^3, R^4, R^5, and R^6 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and the others of R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention; or

one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached forms C(O) or C(=NOH); and the others of R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention.

[00175] In another embodiment of the Invention (A5), the compound of Formula I is selected from Group A where X, R^7, and A are as defined in the Summary of the Invention; and

R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25b})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and

R^1, R^2, R^5 and R^6 are as defined in the Summary of the Invention.

[00176] In another embodiment of embodiment A5, the Compound of Formula I is that where R^1, R^2, R^5 and R^6 are hydrogen.

[00177] In another embodiment of the Invention (A6), the compound of Formula I is selected from Group A where X, R^7, and A are as defined in the Summary of the Invention; and

R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$,

$-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

R^1, R^2, R^5 and R^6 are are as defined in the Summary of the Invention.

[00178] In another embodiment of embodiment A, the Compound of Formula I is that where R^1, R^2, R^5 and R^6 are hydrogen.

[00179] In another embodiment of the Invention (A7), the compound of Formula I is selected from Group A where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen and R^4 is $-NR^8R^{8'}$ (where R^8 is hydrogen, hydroxy, alkyl, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl and $R^{8'}$ is hydroxy, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl), $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alkenyl, and alkynyl; where the alkenyl and alkynyl are optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

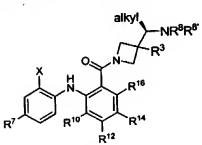
m, $R^{8''}$, and R^9 are as defined in the Summary of the Invention for a compound of Group A; and unless otherwise specified in this embodiment, R^8 and $R^{8'}$ are as defined in the Summary of the Invention for a compound of Group A.

[00180] In another embodiment of the Invention (A8), the compound of Formula I is selected from Group A where R^3 is hydrogen, halo, hydroxy, alkoxy, or amino. In another embodiment, R^3 is hydrogen, fluoro, hydroxy, methoxy, or amino. In another embodiment, R^3 is hydrogen or hydroxy. In another embodiment, R^3 is hydroxy.

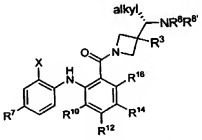
[00181] In another embodiment of embodiment A8, the Compound of Formula I is that where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen; and R^4, is as defined in the Summary of the Invention for a compound of Group A.

[00182] Another embodiment of the Invention (A9) is that where the compound of Formula I is selected from Group A where R^1, R^2, R^5 and R^6 are hydrogen; R^3 is hydrogen, halo, hydroxy, alkoxy, or amino; and R^4 is heterocycloalkyl, heteroaryl, or alkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ and all other groups are as defined in the Summary of the Invention for a compound of Group A.

[00183] In another embodiment of embodiment A9, the Compound of Formula I is that where R^4 is alkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ and all other groups are as defined in the Summary of the Invention for a compound of Group A. In another embodiment, the compound is of Formula I(a) or I(b):



I(a);



I(b)

where R^3 is as defined in A9; X, R^7, R^8, $R^{8'}$, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for a compound of Group A.

[00184] In another embodiment of embodiment A9, the Compound of Formula I is that where R^4 is heterocycloalkyl.

[00185] In another embodiment of embodiment A9, the compound of Formula I is that where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^3 is hydroxy; and R^4 is alkyl substituted with $-NR^8R^{8'}$ or R^4 is heterocycloalkyl optionally substituted with one, two, or three groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and where m, R^3, R^8, $R^{8'}$, $R^{8''}$, and R^9 are as defined in the Summary of the Invention for a compound of Group A.

[00186] In another embodiment of the Invention (A10), the compound of Formula I is selected from Group A where

R^4 is

a) hydrogen;

b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;

c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;

d) $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$;

e) $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$;

f) $-CH_2NR^{25}C(=NH)(R^{25})$;

g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$;

h) alkyl;

i) alkyl substituted with one or two $-OR^8$ where R^8 is hydrogen, aryl, or alkyl where the alkyl is substituted with one or two hydroxy;

j) alkyl substituted with one, two, or three halo;

k) alkyl substituted with nitro;

l) alkyl substituted with $-S(O)_mR^9$ (where m is 0 and R^9 is aryl);

m) alkyl substituted with optionally substituted heterocycloalkyl;

n) alkenyl;

o) $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with optionally substituted heteroaryl; or alkyl substituted with optionally substituted cycloalkyl);

p) -C(O)NR^{8}R$^{8'}$ (where R^{8} is hydrogen, alkyl, or alkenyl; and R$^{8'}$ is hydrogen; hydroxy; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; or optionally substituted alkoxy);

q) -NR^{8}C(O)OR$^{8'}$ (where R^{8} and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl);

r) alkyl substituted with -NR^{8}R$^{8'}$ (where R^{8} is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and R$^{8'}$ is hydrogen; hydroxy; alkoxy; alkyl; alkenyl; alkynyl; optionally substituted alkoxy; alkyl substituted with one or two hydroxy; alkyl substituted with one or two alkoxy; alkyl substituted with -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one or two hydroxy and one or two -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one, two, three, four, or five halo; alkyl substituted with optionally substituted cycloalkyl; alkyl substituted with optionally substituted aryl; alkyl substituted with one or two hydroxy and one optionally substituted aryl; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with optionally substituted heteroaryl; heteroaryl; aryl; aryl substituted with one or two hydroxy; aryl substituted with one or two alkoxy; aryl substituted with one or two halo; aryl substituted with one or two -NR^{32}C(O)R^{32a} where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl; aryl substituted with -NR^{34}SO$_2$R^{34a} where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl; cycloalkyl; cycloalkyl substituted with one or two hydroxy; cycloalkyl substituted with one or two hydroxy and one or two hydroxyalkyl; cycloalkyl substituted with one or two alkoxy; cycloalkyl substituted with carboxy; cycloalkyl substituted with -C(O)NR^{33}R^{33a} where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; alkyl substituted with -C(O)NR^{33}R^{33a} where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; cycloalkyl substituted with optionally substituted cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted with alkyl; heterocycloalkyl substituted with alkoxycarbonyl; heterocycloalkyl substituted with optionally substituted arylalkyl; heterocycloalkyl substituted

with one or two hydroxy; heterocycloalkyl substituted with one or two alkoxy; heterocycloalkyl substituted with one or two hydroxyalkyl; heterocycloalkyl substituted with one or two hydroxy, one or two alkoxy, and one or two hydroxyalkyl; alkyl substituted with optionally substituted aryloxy; alkyl substituted with $-S(O)_nR^{31}$ where n is 0 and R^{31} is alkyl; alkyl substituted with carboxy; alkyl substituted with alkoxycarbonyl; or alkyl substituted with $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl);

s) $-NR^8C(O)R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and $R^{8'}$ is hydrogen; alkyl; alkyl substituted with one or two hydroxy; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, hydroxyalkyl, or alkenyl);

t) cycloalkyl;

u) cycloalkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

v) heterocycloalkyl;

w) heterocycloalkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

x) heterocycloalkyl substituted with one or two alkyl;

y) heterocylcloalkyl substituted with $-C(O)OR^8$ where R^8 is alkyl or alkenyl;

z) alkyl substituted with $-NR^8C(O)R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl and $R^{8'}$ is alkyl; alkenyl; or alkyl substituted with alkoxy, aryl, and one, two, or three halo);

aa) heteroaryl;

bb) heteroaryl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl; alkyl substituted with optionally substituted heteroaryl;

cc) alkyl substituted with $-NR^8S(O)_2R^9$ where R^8 is hydrogen, alkyl, or alkenyl and R^9 is alkyl or alkenyl;

dd) alkyl substituted with $-NR^8C(O)OR^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

ee) alkyl substituted with one aryl and one $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl; or

ff) alkyl substituted with one or two $-OR^8$ (where R^8 is hydrogen) and one or two $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl.

[00187] In another embodiment, R^4 is hydrogen, $-CH_2N(H)(NHCH_3)$, $-CH_2NHC(=NH)(NH_2)$, $-CH_2NHC(=NH)(NHNO_2)$, $-CH_2NHC(=NH)(NHCN)$, $-CH_2NHC(=NH)$(phenyl), $-CH_2NHC(NH_2)=CH(NO_2)$, methyl, ethyl, hydroxymethyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-prop-2-yl, *N*-(1-methoxy-prop-2-yl)-aminomethyl, *N*-(ethoxypropyl)-aminomethyl, *N*-(ethoxyethyl)-aminomethyl, *N*-(2,2-dimethoxyethyl)-aminomethyl, *N*-(methoxyethyl)-aminomethyl, *N*-(isopropxyethyl)-aminomethyl, trifluoromethyl, 1-nitro-ethyl, 1-methyl-1-nitro-ethyl, 1-nitro-propyl, 3-methyl-1-nitro-butyl, phenylthiomethyl, allyl, ethenyl, 2-methylthio-ethylaminomethyl, 3-methylthio-propylaminomethyl, *N*-(*tert*-butoxycarbonylaminopropyl)-aminomethyl, *N*-(1-carboxyethyl)-aminomethyl, *N*-(1*R*-carboxyethyl)-aminomethyl, *N*-(1*S*-carboxyethyl)-aminomethyl, *N*-(1-methoxycarbonylethyl)-aminomethyl, $-NH_2$, $-NH(CH_2)_3CH_3$, $-NHCH_3$, $-NH(CH_2CH_3)$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2CH_2NH_2$, $-N(CH_3)CH_2CH_2$(heteroaryl), $-NHCH_2$(cycloalkyl), $-C(O)NH_2$, $-C(O)NHOH$, $-C(O)NH(OCH_2CH(OH)CH_2OH)$, $-C(O)NH(CH_2)_3CH_3$, $-C(O)NHCH_2CH{=}CH_2$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH_2CH_2OH$, $-C(O)NHCH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2$(piperidin-1-yl), $-C(O)NH$(phenyl), $-C(O)NHCH_2CH_2N(CH_2CH_3)_2$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_3$, azetidinylmethyl, pyrrolidinylmethyl, 3-hydroxy-pyrrolidinylmethyl, 2-(methoxymethyl)-pyrrolidinylmethyl, 2*S*-(methoxymethyl)-pyrrolidinylmethyl, 2*R*-(methoxymethyl)-pyrrolidinylmethyl, morpholinylmethyl, hydroxypiperidinylmethyl, 4-alkyl-piperazinylmethyl, 4-alkyl-homopiperazinylmethyl, 4-(heterocycloalkyl)-piperidinylmethyl, 4-(dialkylaminoalkyl)-piperazinylmethyl, *N*-hydroxyaminomethyl, *N*-methoxyaminomethyl, *N*-ethoxyaminomethyl, *N*-ethylaminomethyl, 1-(*N*-ethyl-amino)-ethyl, *N,N*-diethylaminomethyl, *N,N*-dimethylaminomethyl, aminomethyl, 1-amino-ethyl, 1*R*-amino-ethyl, 1*S*-amino-ethyl, 1-(methylamino)-ethyl, 1-(*N,N*-dimethylamino)-ethyl, 1-amino-1-methyl-ethyl, 1-aminopropyl, 1*S*-aminopropyl, 1*R*-aminopropyl, *N*-(n-propyl)-aminomethyl, *N*-(isopropyl)-aminomethyl, 2-(*N*-isopropylamino)-ethyl, 3-(*N*-isopropylamino)-2-methyl-prop-2-yl, 1-(*N*-ethyl-amino)-propyl, 1-(*N,N*-diethyl-amino)-propyl, 1-aminobutyl, 1-amino-isobutyl, *N*-(2-aminoethyl)-aminomethyl, *N*-(n-butyl)-aminomethyl, *N*-isobutylaminomethyl, *tert*-butylaminomethyl, 1-(*tert*-butylamino)-ethyl,

sec-butylaminomethyl, *N*-(2-methyl-but-3-yl)-aminomethyl, *N*-(3,3-dimethyl-butyl)-aminomethyl, *N*-(3-methylbut-3-yl)-aminomethyl, *N*-(2-methylbutyl)-aminomethyl, *N*-(pent-3-yl)-aminomethyl, n-pentylaminomethyl, isopentylaminomethyl, *sec*-pentylaminomethyl, neopentylaminomethyl, *N*-(2,2,4-trimethyl-pent-4-yl)-aminomethyl, *N*-(2-ethyl-butyl)-aminomethyl, *N*-allyl-aminomethyl, 3-methyl-but-1-yn-3-ylaminomethyl, *N*-(2,3-dihydroxypropyloxy)-aminomethyl, *N*-cyclopropylaminomethyl, *N*-cyclobutylaminomethyl, *N*-cyclopentylaminomethyl, *N*-cyclopenten-4-ylaminomethyl, *N*-(1(*R*,*S*)-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1(*R*,*S*)-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(3,4-dihydroxy-cyclopentyl)-aminomethyl, *N*-(1-hydroxymethyl-cyclopent-1-yl)-aminomethyl, *N*-(2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-aminomethyl, *N*-(1(*R*,*S*)-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1-carboxy-cyclopentyl)-aminomethyl, *N*-cyclohexylaminomethyl, *N*-(1(*R*,*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(*cis*-4-hydroxy-cyclohexyl)-aminomethyl, *N*-(*trans*-4-hydroxy-cyclohexyl)-aminomethyl, 1-[*N*-(*cis*-4-hydroxy-cyclohexyl)-amino]-ethyl, 1-[*N*-(*trans*-4-hydroxy-cyclohexyl)-amino]-ethyl, *N*-(1(*R*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1(*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1-hydroxymethyl-cyclohexyl)-aminomethyl, *N*-(2-cyclohexyl-cyclohexyl)-aminomethyl, *N*-{(2*R*,3*S*,4*R*,6*R*)-2-(hydroxymethyl)-3,4-dihydroxy-6-methoxy-tetrahydro-2*H*-pyran-5-yl}-aminomethyl, *N*-(cycloheptyl)-aminomethyl, *N*-(cyclooctyl)-aminomethyl, [(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1^{3,7}]dec-2-ylamino]methyl, *N*-[1-(cyclopropylaminocarbonyl)-cyclopentyl]-aminomethyl, -$CH_2NHC(CH_3)_2C(O)NH$(cyclohexyl), -$CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, *N*-(1-benzyloxy-cyclopent-2-yl)-aminomethyl, *N*-(cyclopropylmethyl)-aminomethyl, *N*-(cyclohexylmethyl)-aminomethyl, *N*-(1-cyclohexylethyl)-aminomethyl, *N*-(imidazolyl)-aminomethyl, *N*-(1,3,5-triazinyl)-aminomethyl, *N*-(5-hydroxy-pyrazol-3-yl)-aminomethyl, *N*-(5-methyl-pyrazol-3-yl)-aminomethyl, *N*-(benzimidazolyl)-aminomethyl, *N*-(pyrimidin-2-yl)-aminomethyl, *N*-(pyridin-2-yl)-aminomethyl, *N*-(pyridin-3-yl)-aminomethyl, *N*-(pyridin-4-yl)-aminomethyl, *N*-indan-1-yl-aminomethyl, *N*-indan-2-yl-aminomethyl, phenylaminomethyl, *N*-(2-hydroxyphenyl)-aminomethyl, *N*-(3-hydroxyphenyl)-aminomethyl, *N*-(4-

hydroxyphenyl)-aminomethyl, *N*-(2-methoxyphenyl)-aminomethyl, *N*-(3-methoxyphenyl)-aminomethyl, *N*-(4-methoxyphenyl)-aminomethyl, *N*-(2-fluorophenyl)-aminomethyl, *N*-(3-fluorophenyl)-aminomethyl, *N*-(4-fluorophenyl)-aminomethyl, *N*-(2-chlorophenyl)-aminomethyl, *N*-(3-chlorophenyl)-aminomethyl, *N*-(4-chlorophenyl)-aminomethyl, *N*-(3-methylcarbonylamino-phenyl)-aminomethyl, *N*-(4-methylcarbonylamino-phenyl)-aminomethyl, *N*-(2-aminophenyl)-aminomethyl, *N*-(3-aminophenyl)-aminomethyl, *N*-(4-aminophenyl)-aminomethyl, *N*-(2-methylsulfonylaminophenyl)-aminomethyl, *N*-(3-methylsulfonylaminophenyl)-aminomethyl, *N*-(4-methylsulfonylaminophenyl)-aminomethyl, *N*-(2-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(3-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(benzyl)-aminomethyl, *N*-(2-hydroxyphenylmethyl)-aminomethyl, *N*-(3-hydroxyphenylmethyl)-aminomethyl, *N*-(4-hydroxyphenylmethyl)-aminomethyl, *N*-(2-(*N*-methylpiperazin-1-yl)-phenylmethyl)-aminomethyl, *N*-(4-alkyl-phenethyl)-aminomethyl, *N*-(1-hydroxy-3-phenyl-prop-2-yl)-aminomethyl, *N*-(pyrrolidin-2-ylmethyl)-aminomethyl, *N*-(*N*-alkyl-pyrrolidinylmethyl)-aminomethyl, *N*-(*N*-alkyl-pyrrolidinylethyl)-aminomethyl, *N*-(pyrrolidinylpropyl)-aminomethyl, *N*-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-aminomethyl, *N*-(tetrahydrofuranylmethyl)-aminomethyl, *N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-aminomethyl, *N*-(tetrahydro-2*H*-pyranylethyl)-aminomethyl, *N*-(piperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-*tert*-butoxycarbonylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-4-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-5-ylmethyl)-aminomethyl, *N*-[2-(imidazol-4-yl)-ethyl]-aminomethyl, *N*-[3-(imidazolyl)-propyl]-aminomethyl, *N*-(pyridin-3-ylethyl)-aminomethyl, *N*-(pyridin-4-ylethyl)-aminomethyl, *N*-(thien-2-ylethyl)-aminomethyl, *N*-(furan-2-ylethyl)-aminomethyl, *N*-(5-methyl-1,3,4-oxadiazol-2-ylmethyl)-aminomethyl, *N*-(2-indolin-3-ylethyl)-aminomethyl, 2-(*N*,*N*-dimethylamino)-ethylaminomethyl, 2-(*N*,*N*-dimethylamino)-1-methyl-ethylaminomethyl, 3-aminopropylaminomethyl, 3-(*N*,*N*-dimethylamino)-propylaminomethyl, 3-(*N*,*N*-diethylamino)-propylaminomethyl, *N*-(*N*,*N*-diisopropylaminoethyl)-aminomethyl, *N*-(*N*,*N*-dimethylaminobutyl)-aminomethyl, *N*-(3-hydroxypropyl)-aminomethyl, *N*-(2-hydroxypropyl)-aminomethyl, *N*-(1,2-dihydroxypropyl)-aminomethyl, *N*-(1-amino-2-hydroxy-prop-3-yl)-aminomethyl, *N*-(*N*-ethoxycarbonyl-piperidin-4-yl)-aminomethyl, *N*-(*N*-benzylpiperidin-4-yl)-aminomethyl, *N*-(homopiperidin-3-yl)-aminomethyl, *N*-(*N*-benzylpyrrolidin-3-yl)-aminomethyl, *N*-(*N*-ethylpiperidin-3-yl)aminomethyl,

2,2,2-trifluoroethylaminomethyl, 3,3,3-trifluoropropylaminomethyl, 2,2,3,3,3-pentafluoropropylaminomethyl, $-CH_2N(CH_2CH_2OH)_2$, $-CH_2N(CH_3)(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2CH_2CH_2OH)$, $-CH_2N(CH_3)$(*N*-methyl-pyrrolidin-3-yl), $-CH_2NH(C(CH_3)_2CH_2OH)$, $-NHC(O)CH(CH_3)_2$, $-NHC(O)CH_2N(CH_2CH_3)_2$, $-NHC(O)CH_2NH(CH_3)$, -NHC(O)H, $-NHC(O)CH_2CH(OH)CH_2OH$, $-NHC(O)CH_2NH_2$, $-NHC(O)CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2$(4-alkyl-piperazinyl), $-NHC(O)CH_2$(piperidinyl), *N*-(phenyloxyethyl)-aminomethyl, cyclopentyl, 1-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, *cis*-2-amino-cyclopentyl, *trans*-2-amino-cyclopentyl, (*cis,trans*)-2-hydroxy-cyclohexyl, *cis*-2-hydroxy-cyclohexyl, *trans*-2-hydroxy-cyclohexyl, (*cis,trans*)-2-amino-cyclohexyl, *cis*-2-amino-cyclohexyl, *trans*-2-amino-cyclohexyl, azetidin-3-yl, pyrrolidinyl, *N*-alkyl-pyrrolidinyl, 3-(dialkylamino)-pyrrolidinyl, piperidinyl, 2-methyl-piperidin-6-yl, *N*-*tert*-butoxycarbonylpiperidin-2-yl, piperazinyl, $-CH_2NHC(O)CH_3$, $-CH(CH_3)NHC(O)CH_3$, $-CH(CH_3)NHC(O)C(OCH_3)(CF_3)$phenyl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, *N*-methyl-imidazol-2-yl, 5-methyl-imidazol-2-yl, 1,2,4-triazol-3-yl, thiazol-2-yl, 2-aminopyrimidin-3-yl, pyridinyl, benzimidazolyl, imidazol-1-ylmethyl, imidazol-2-ylmethyl, triazolylmethyl, (5-amino-3-methylpyrazol-1-yl)-methyl, phenoxymethyl, methylsulfonylaminomethyl, 1-(methoxycarbonylamino)-ethyl, 1-amino-1-phenyl-methyl, or 1-amino-3-hydroxy-propyl.

[00188] In another embodiment of embodiment A10, the Compound of Formula I is that where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen; and R^3 is hydrogen, halo, hydroxy, alkoxy, or amino.

[00189] In another embodiment of embodiment A10, the Compound of Formula I is that where R^3 is hydrogen and R^4 is

a) hydrogen;

b) $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with optionally substituted heteroaryl; or alkyl substituted with optionally substituted cycloalkyl);

c) -C(O)NR^{8}R$^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and R$^{8'}$ is hydrogen; hydroxy; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with heterocycloalkyl; alkyl substituted with -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; or optionally substituted alkoxy);

d) -NR^{8}C(O)OR$^{8'}$ (where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl);

e) -NR^{8}C(O)R$^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and R$^{8'}$ is hydrogen; alkyl; alkyl substituted with one or two hydroxy; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, hydroxyalkyl, or alkenyl);

f) alkyl;

g) alkyl substituted with one or two -OR^8 (where R^8 is hydrogen);

h) alkyl substituted with -NR^{8}R$^{8'}$ (where R^8 is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and R$^{8'}$ is hydrogen; alkyl; alkenyl; alkynyl; alkyl substituted with one or two hydroxy; heterocycloalkyl substituted with alkyl; or alkyl substituted with -NR^{30}R$^{30'}$ where R^{30} and R$^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl);

i) heterocycloalkyl; or

j) heterocycloalkyl substituted with -NR^{8}R$^{8'}$ (where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00190] In another embodiment, R^3 is hydrogen and R^4 is hydrogen, hydroxymethyl, -NH$_2$, -NH(CH$_2$)$_3$CH$_3$, -NHCH$_3$, -NH(CH$_2$CH$_3$), -NHCH$_2$CH(CH$_3$)$_2$, -NHCH$_2$CH$_2$OH, -NHCH$_2$CH$_2$CH$_2$NH$_2$, -N(CH$_3$)CH$_2$CH$_2$(pyridin-2-yl), -NHCH$_2$(cyclopropyl), -NHCH$_2$(cyclopentyl), -NHCH$_2$(cyclohexyl), -C(O)NHOH, -C(O)NH(OCH$_2$CH(OH)CH$_2$OH), -C(O)NH(CH$_2$)$_3$CH$_3$, -C(O)NHCH$_2$CH=CH$_2$, -C(O)NHCH$_2$CH$_3$, -C(O)NHCH$_2$CH$_2$OH, -C(O)NHCH$_2$CH(OH)CH$_2$OH, -C(O)NHCH$_2$CH$_2$CH(OH)CH$_2$OH, -C(O)NHCH$_2$CH$_2$(piperidin-1-yl), -C(O)NH(phenyl), -C(O)NHCH$_2$CH$_2$N(CH$_2$CH$_3$)$_2$, *N*-(isopropyl)-aminomethyl, *N*,*N*-dimethylaminomethyl, *N*-(2-aminoethyl)-aminomethyl, -NHC(O)OC(CH$_3$)$_3$, -NHC(O)OCH$_3$, -NHC(O)CH(CH$_3$)$_2$, -NHC(O)CH$_2$NH$_2$, -NHC(O)CH$_2$N(CH$_2$CH$_3$)$_2$, -NHC(O)CH$_2$NH(CH$_3$), -NHC(O)H, -NHC(O)CH$_2$CH(OH)CH$_2$OH, -NHC(O)CH$_2$N(CH$_2$CH$_2$OH)$_2$, -NHC(O)CH$_2$CH$_2$N(CH$_2$CH$_2$OH)$_2$, -NHC(O)CH$_2$(4-alkyl-piperazinyl), -NHC(O)CH$_2$(piperidinyl), pyrrolidinyl,

3-(dialkylamino)-pyrrolidinyl, piperidinyl, 2-methyl-piperidin-6-yl, *N*-methylpiperidin-2-yl, or piperazin-2-yl.

[00191] In another embodiment of embodiment A10, the Compound of Formula I is that where R^3 is alkoxy and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl). In another embodiment, R^3 is methoxy and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00192] In another embodiment of embodiment A10, the Compound of Formula I is that where R^3 is halo and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl). In another embodiment, R^3 is fluoro and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00193] In another embodiment of embodiment A10, the Compound of Formula I is that where R^3 is amino and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00194] In another embodiment of embodiment A10, the Compound of Formula I is that where R^3 is hydroxy and R^4 is

a) hydrogen;
b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;
c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;
d) $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2)$;
e) $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN)$;
f) $-CH_2NR^{25}C(=NH)(R^{25})$;
g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$;
h) alkyl;
i) alkenyl;
j) alkyl substituted with one or two $-OR^8$ where R^8 is hydrogen, aryl, or alkyl where the alkyl is substituted with one or two hydroxy;
k) alkyl substituted with one, two, or three halo;
l) alkyl substituted with nitro;
m) alkyl substituted with $-S(O)_mR^9$ (where m is 0 and R^9 is aryl);
n) alkyl substituted with optionally substituted heterocycloalkyl;
o) alkyl substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and $R^{8'}$ is hydrogen; hydroxy;

alkoxy; alkyl; alkenyl; alkynyl; optionally substituted alkoxy; alkyl substituted with one or two hydroxy; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one or two hydroxy and one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; heterocycloalkyl substituted with alkyl, alkoxycarbonyl, or optionally substituted arylalkyl; alkyl substituted with one, two, three, four, or five halo; alkyl substituted with optionally substituted cycloalkyl; alkyl substituted with optionally substituted aryl; alkyl substituted with one or two hydroxy and one optionally substituted aryl; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with optionally substituted heteroaryl; heteroaryl; aryl; aryl substituted with one or two hydroxy; aryl substituted with one or two alkoxy; aryl substituted with one or two halo; aryl substituted with one or two $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl; aryl substituted with $-NR^{34}SO_2R^{34a}$ where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl; cycloalkyl; cycloalkyl substituted with one or two hydroxy; cycloalkyl substituted with one or two hydroxy and one or two hydroxyalkyl; cycloalkyl substituted with one or two alkoxy; cycloalkyl substituted with carboxy; cycloalkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; cycloalkyl substituted with optionally substituted cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted with one or two hydroxy; heterocycloalkyl substituted with one or two alkoxy; heterocycloalkyl substituted with one or two hydroxyalkyl; heterocycloalkyl substituted with one or two hydroxy, one or two alkoxy, and one or two hydroxyalkyl; alkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; alkyl substituted with optionally substituted aryloxy; alkyl substituted with $-S(O)_nR^{31}$ where n is 0 and R^{31} is alkyl; alkyl substituted with carboxy; alkyl substituted with alkoxycarbonyl; or alkyl substituted with $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl);

p) heterocycloalkyl;

q) -C(O)NR^{8}R$^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and R$^{8'}$ is hydrogen; alkyl; alkyl; alkenyl; or substituted with one or two hydroxy;);

r) alkyl substituted with -NR^{8}C(O)R$^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl and R$^{8'}$ is alkyl; alkenyl; or alkyl substituted with alkoxy, aryl, and one, two, or three halo);

s) cycloalkyl;

t) cycloalkyl substituted with -NR^{8}R$^{8'}$ where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl;

u) cycloalkyl substituted with -C(O)NR^{33}R^{33a} where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl;

v) heterocycloalkyl;

w) heterocycloalkyl substituted with one or two alkyl;

x) heterocylcloalkyl substituted with -C(O)OR^8 where R^8 is alkyl or alkenyl;

y) heteroaryl;

z) heteroaryl optionally substituted with -NR^{8}R$^{8'}$ where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl;

aa) alkyl substituted with optionally substituted heteroaryl;

bb) alkyl substituted with -NR^{8}S(O)$_2$R^9 where R^8 is hydrogen, alkyl, or alkenyl and R^9 is alkyl or alkenyl;

cc) alkyl substituted with -NR^{8}C(O)OR$^{8'}$ where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl;

dd) alkyl substituted with one aryl and one -NR^{8}R$^{8'}$ where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl; or

ee) alkyl substituted with one or two -OR^8 (where R^8 is hydrogen) and one or two -NR^{8}R$^{8'}$ where R^8 and R$^{8'}$ are independently hydrogen, alkyl, or alkenyl.

[00195] In another embodiment, R^3 is hydroxy and R^4 is hydrogen, -CH$_2$N(H)(NHCH$_3$), -CH$_2$NHC(=NH)(NH$_2$), -CH$_2$NHC(=NH)(NHNO$_2$), -CH$_2$NHC(=NH)(NHCN), -CH$_2$NHC(=NH)(phenyl), -CH$_2$NHC(NH$_2$)=CH(NO$_2$), methyl, ethyl, hydroxymethyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-prop-2-yl, *N*-(1-methoxy-prop-2-yl)-aminomethyl, *N*-(ethoxypropyl)-aminomethyl, *N*-(ethoxyethyl)-aminomethyl, *N*-(2,2-dimethoxyethyl)-aminomethyl, *N*-(methoxyethyl)-aminomethyl, *N*-(isopropxyethyl)-aminomethyl, trifluoromethyl, 1-nitro-ethyl, 1-methyl-1-nitro-ethyl, 1-nitro-propyl, 3-methyl-1-nitro-butyl, phenylthiomethyl, allyl, ethenyl, 2-methylthio-ethylaminomethyl, 3-methylthio-

propylaminomethyl, *N*-(*tert*-butoxycarbonylaminopropyl)-aminomethyl, *N*-(1-carboxyethyl)-aminomethyl, *N*-(1*R*-carboxyethyl)-aminomethyl, *N*-(1*S*-carboxyethyl)-aminomethyl, *N*-(1-methoxycarbonylethyl)-aminomethyl, azetidinylmethyl, pyrrolidinylmethyl, 3-hydroxy-pyrrolidinylmethyl, 2-(methoxymethyl)-pyrrolidinylmethyl, 2*S*-(methoxymethyl)-pyrrolidinylmethyl, 2*R*-(methoxymethyl)-pyrrolidinylmethyl, morpholinylmethyl, 4-hydroxypiperidinylmethyl, 4-methyl-piperazinylmethyl, 4-methyl-homopiperazinylmethyl, 4-(piperidinyl)-piperidinylmethyl, 4-[2-(*N*,*N*-diethylamino)-ethyl]-piperazinylmethyl, *N*-hydroxyaminomethyl, *N*-methoxyaminomethyl, *N*-ethoxyaminomethyl, *N*-ethylaminomethyl, 1-(*N*-ethyl-amino)-ethyl, *N*,*N*-diethylaminomethyl, *N*,*N*-dimethylaminomethyl, aminomethyl, 1-amino-ethyl, 1*R*-amino-ethyl, 1*S*-amino-ethyl, 1-(methylamino)-ethyl, 1-(*N*,*N*-dimethylamino)-ethyl, 1-amino-1-methyl-ethyl, 1-aminopropyl, 1*S*-aminopropyl, 1*R*-aminopropyl, *N*-(n-propyl)-aminomethyl, *N*-(isopropyl)-aminomethyl, 2-(*N*-isopropylamino)-ethyl, 3-(*N*-isopropylamino)-2-methyl-prop-2-yl, 1-(*N*-ethyl-amino)-propyl, 1-(*N*,*N*-diethyl-amino)-propyl, 1-aminobutyl, 1-amino-isobutyl, *N*-(n-butyl)-aminomethyl, *N*-isobutylaminomethyl, *tert*-butylaminomethyl, 1-(*tert*-butylamino)-ethyl, *sec*-butylaminomethyl, *N*-(2-methyl-but-3-yl)-aminomethyl, *N*-(3,3-dimethyl-butyl)-aminomethyl, *N*-(3-methylbut-3-yl)-aminomethyl, *N*-(2-methylbutyl)-aminomethyl, *N*-(pent-3-yl)-aminomethyl, n-pentylaminomethyl, isopentylaminomethyl, *sec*-pentylaminomethyl, neopentylaminomethyl, *N*-(2,2,4-trimethyl-pent-4-yl)-aminomethyl, *N*-(2-ethyl-butyl)-aminomethyl, *N*-allyl-aminomethyl, 3-methyl-but-1-yn-3-ylaminomethyl, *N*-(2,3-dihydroxypropyloxy)-aminomethyl, *N*-cyclopropylaminomethyl, *N*-cyclopentylaminomethyl, *N*-cyclopenten-4-ylaminomethyl, *N*-(1(*R*,*S*)-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1(*R*,*S*)-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(3,4-dihydroxy-cyclopentyl)-aminomethyl, *N*-(1-hydroxymethyl-cyclopent-1-yl)-aminomethyl, *N*-(2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-aminomethyl, *N*-(1(*R*,*S*)-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1-carboxy-cyclopentyl)-aminomethyl, *N*-cyclohexylaminomethyl, *N*-(1(*R*,*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1(*R*)-hydroxy-cyclohex-2-yl)-aminomethyl,

N-(1(*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(*cis*-4-hydroxy-cyclohexyl)-aminomethyl, *N*-(*trans*-4-hydroxy-cyclohexyl)-aminomethyl, 1-[*N*-(*cis*-4-hydroxy-cyclohexyl)-amino]-ethyl, 1-[*N*-(*trans*-4-hydroxy-cyclohexyl)-amino]-ethyl, *N*-(1-hydroxymethyl-cyclohexyl)-aminomethyl, *N*-(2-cyclohexyl-cyclohexyl)-aminomethyl, *N*-{(2*R*,3*S*,4*R*,6*R*)-2-(hydroxymethyl)-3,4-dihydroxy-6-methoxy-tetrahydro-2*H*-pyran-5-yl}-aminomethyl, *N*-(cycloheptyl)-aminomethyl, *N*-(cyclooctyl)-aminomethyl, [(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1^{3,7}]dec-2-ylamino]methyl, *N*-(1-benzyloxy-cyclopent-2-yl)-aminomethyl, *N*-[1-(cyclopropylaminocarbonyl)-cyclopentyl]-aminomethyl, -$CH_2NHC(CH_3)_2C(O)NH$(cyclohexyl), -$CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, *N*-(cyclopropylmethyl)-aminomethyl, *N*-(cyclohexylmethyl)-aminomethyl, *N*-(1-cyclohexylethyl)-aminomethyl, *N*-(imidazolyl)-aminomethyl, *N*-(1,3,5-triazinyl)-aminomethyl, *N*-(5-hydroxy-pyrazol-3-yl)-aminomethyl, *N*-(5-methyl-pyrazol-3-yl)-aminomethyl, *N*-(benzimidazolyl)-aminomethyl, *N*-(pyrimidin-2-yl)-aminomethyl, *N*-(pyridin-2-yl)-aminomethyl, *N*-(pyridin-3-yl)-aminomethyl, *N*-(pyridin-4-yl)-aminomethyl, *N*-indan-1-yl-aminomethyl, *N*-indan-2-yl-aminomethyl, phenylaminomethyl, *N*-(2-hydroxyphenyl)-aminomethyl, *N*-(3-hydroxyphenyl)-aminomethyl, *N*-(4-hydroxyphenyl)-aminomethyl, *N*-(2-methoxyphenyl)-aminomethyl, *N*-(3-methoxyphenyl)-aminomethyl, *N*-(4-methoxyphenyl)-aminomethyl, *N*-(2-fluorophenyl)-aminomethyl, *N*-(3-fluorophenyl)-aminomethyl, *N*-(4-fluorophenyl)-aminomethyl, *N*-(2-chlorophenyl)-aminomethyl, *N*-(3-chlorophenyl)-aminomethyl, *N*-(4-chlorophenyl)-aminomethyl, *N*-(3-methylcarbonylamino-phenyl)-aminomethyl, *N*-(4-methylcarbonylamino-phenyl)-aminomethyl, *N*-(2-aminophenyl)-aminomethyl, *N*-(3-aminophenyl)-aminomethyl, *N*-(4-aminophenyl)-aminomethyl, *N*-(2-methylsulfonylaminophenyl)-aminomethyl, *N*-(3-methylsulfonylaminophenyl)-aminomethyl, *N*-(4-methylsulfonylaminophenyl)-aminomethyl, *N*-(2-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(3-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(benzyl)-aminomethyl, *N*-(2-hydroxyphenylmethyl)-aminomethyl, *N*-(3-hydroxyphenylmethyl)-aminomethyl, *N*-(4-hydroxyphenylmethyl)-aminomethyl, *N*-(2-(*N*-methylpiperazin-1-yl)-phenylmethyl)-aminomethyl, *N*-(4-methyl-phenethyl)-aminomethyl, *N*-(1-hydroxy-3-phenyl-prop-2-yl)-aminomethyl, *N*-(pyrrolidin-2-ylmethyl)-aminomethyl, *N*-(*N*-ethyl-pyrrolidinylmethyl)-aminomethyl, *N*-(*N*-methyl-pyrrolidin-2-ylethyl)-aminomethyl, *N*-(pyrrolidinylpropyl)-aminomethyl, *N*-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-aminomethyl, *N*-(tetrahydrofuranylmethyl)-